Università degli Studi di Urbino Carlo Bo
Dipartimento di Scienze Biomolecolari

Dottorato di Ricerca in Scienze Chimiche e Scienze Farmaceutiche
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Coordinatore Dottorato: Chiar.mo Prof. G. Spadoni

Oxidative Carbonylation of Unsaturated Substrates Promoted by Aryl α-Diimine Pd(II) Complexes

Settore Disciplinare Chim/03

Dottoranda:
Michela Beltrani

Relatore:
Chiar.mo Prof. G. Spadoni

Co-Relatore:
Chiar.ma Prof. ssa C. Carfagna
Dr. F. Fini

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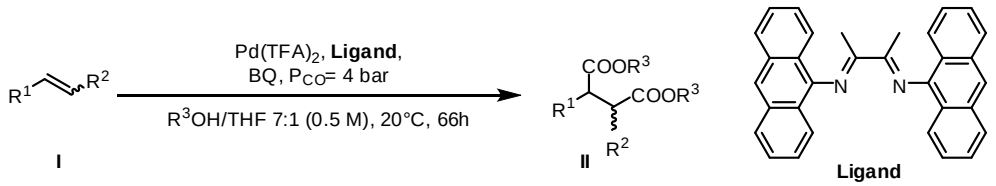
Section II: Towards the Development of a New Strategy of the Synthesis of ^{18}F-FAC

1. Preface

The argument that has interested me during the period spent as a PhD student is essentially focused on the catalytic oxidative carbonylation.

The importance of this kind of reaction is described across the general introduction. It started from a general overture around the most important process, that describe the importance of homogeneous catalysis in the organometallic chemistry, following by a briefly description of the fundamental role of palladium in this field. Indeed, oxidative carbonylation reactions can be promoted by palladium complexes and are able to convert simple and widespread substrates as alkenes and alkynes into highly functionalized carbonyl compounds.

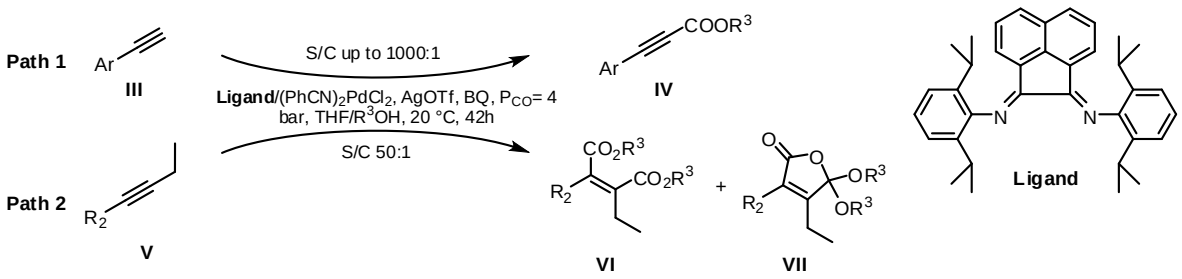
A new and selective methodology for the bis-alcoxycarbonylation of alkenes has been developed in the group in which I spent my PhD and is described in the fifth chapter of section I (Scheme I). Olefins **I** are converted into the succinic diesters derivatives **II** in good yield and high selectivity thanks to aril α-diimine palladium complex, formed *in situ*, in the presence of a nucleophiles and organic oxidant.



Scheme I. Oxidative carbonylation of alkenes.

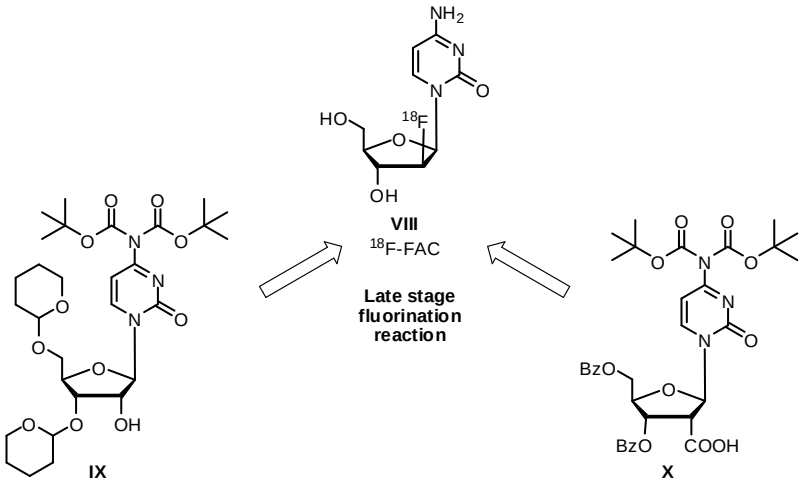
The method can be transferred into the oxidative carbonylation of alkynes **III** (section I, chapter sixth). In particular, phenylacetylenes with substituents on the aromatic ring can be mono-alkoxycarbonylated into propiolic esters **IV** with high selectivity and modest to good yields (Scheme II, Path 1).

While the 1-phenyl-1-butyne and hex-3-yne **V**, in the same reaction conditions used for the terminal alkynes, for the first time, can be converted into two bis-alkoxycarbonyl products **VI**, **VII** (Scheme II, Path 2).



Scheme II. Oxidative carbonylation of alkynes.

At the beginning of my third year of PhD studies, I spent six months in the group of Prof. Tobias Ritter, at the Department of Chemistry and Biological Chemistry, Harvard University (Section II).
During this fruitful period I have been involved in a project concerning the synthesis of useful precursors **IX**, **X** for the achievement of one of the currently most promising probes ^{18}F-FAC **VIII** for positron emission tomography (PET) across the late stage fluorination step (Scheme III).



Scheme III. Precursors for the late stage fluorination step.

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List of pubblications:

M. Beltrani, C. Carfagna, B. Milani, R. Mancuso, B. Gabriele, F. Fini "Oxidative Alkoxycarbonylation of Acetylenes by Means of Aryl α-diimine Pd(II) Complexes as Catalysts". *Manuscript in Preparation*

F. Fini, M. Beltrani, R. Mancuso, B. Gabriele, C. Carfagna.
"Highly Selective Aryl α-Diimine/Palladium-Catalyzed Bis-Alkoxycarbonylation of Olefins for the Synthesis of Substituted Succinic Diesters" *Adv. Synth. Catal*. **2015**, *357*, 177–184.

Conference Proceedings:

Michela Beltrani, Francesco Fini, Carla Carfagna, "Efficient Aryl alfa-Diimine Pd(II) Catalyst For Alkozycarbonylation of Alkenes and Alkynes" Tuma 2014, Pesaro, 16-18 September 2014.

Michela Beltrani, Francesco Fini, Carla Carfagna , "Efficient Aryl -Diimine Pd(II) Catalyst for the Selective Alkoxycarbonylation of Alkenes and Alkynes" SAYCS 2013, Riccione, 28-30 October 2013.

Francesco Fini, Michela Beltrani, Carla Carfagna, "Higly Selective Carbonylation Reaction of Unsaturated Molecules Catalyzed by Aryl -Diimine Pd (II) Complexes" TUMA 2013, Sesto Fiorentino (FI), 1-2 July 2013.

2. List of Abbreviations

^{18}F-FAC	1-(2’-deoxy-2’-fluoroarabinofuranosyl)cytosine
δ	chemical shift
Ac	acetyl
AIBN	azobisisobutyronitrile
Alk	alkyl
Ar	aryl
BIAN	Bis(imino)acenaphthenes
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-Butyloxycarbonyl
Bn	benzyl
BQ	benzoquinone
Bz	benzoyl
DAB	N,N-diaryl-diazabutadiene
DCE	1,2-dichloroethene
dCK	deoxycytidine kinase
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DiPAMP	ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
DIPEA	diisopropylathylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	dess–Martin periodinane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl
H	hour
i-Pr	*i*-propyl
L	ligand
LDA	Lithium diisopropylamide
L-DOPA	(S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid
LiHMDS	lithium bis(trimethylsilyl)amide
m	*meta*
M	metal
Me	methyl
Ms	mesyl
NaHMDS	sodium bis(trimethylsilyl)amide
n-Bu	*n*-butyl

NMO	N-methylmorpholine-N-Oxide
o	*ortho*
Ox	oxidant
p	*para*
PET	positron emission tomography
PG	protecting group
PGMs	platinum-group metals
Ph	phenyl
Ph_3P	triphenylphosphine
PhNTf	N-Phenyl-bis(trifluoromethanesulfonimide)
Pin_2B_2	bis(pinacolato)diboron
PMB	4-Methoxybenzyl
ppm	parts per million
p-TsOH	p-Toluenesulfonic acid
Py	pyridine
S/C	substrate catalyst ratio
SHOP	shell higher olefin process
TBAF	tetra-n-butylammonium fluoride
t-Bu	*t*-butyl
TBS	*tert*-butyldimethylsilyl
TDCPP	5, 10, 15, 20-tetrakis(2,6-dichlorophenyl)porphyrin
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMP	tetramesitylporphyrin
TOF	turn over frequency
TON	turnover number
$TIPDSiCl_2$	1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane
TPFPP	5, 10, 15, 20-tetrakis(2,6-pentafluorophenyl)porphyrin
TPP	tetraphenylporphyrin
TTP	5, 10, 15, 20-tetrakis(*p*-tolyl)porphyrin
Tr	trityl

Section 1

Oxidative Carbonylation of Unsaturated Substrates Promoted by Aryl α-Diimine Pd(II) Complexes

3. General introduction

3.1 Organometallic Chemistry and Homogenous Catalysis

Organometallic compounds (metal organyls, organometallics) are defined as molecules, which maintain direct bonds between metal and carbon atoms $M^{\delta+} - C^{\delta-}$.[1] In addition to the traditional metals, lanthanides, actinides and semimetals, elements such as boron, silicon, and selenium, are considered to form organometallic compounds.

The study of organometallic compound has contributed significantly both to chemical theory and to practice. Consequently, in 1853 Frankland investigated the properties of ethylzinc iodide and of diethylzinc making the first clear statement of the theory of valency. In 1900, from a more functional approach, Grignard reagents readily endowed managed and versatile intermediates to organic syntheses. In addition, the study of aluminum alkyls has led to their use in catalysts for the large-scale polymerization and oligomerization of olefins.

Reagents and complexes containing transition metal are noteworthy in modern organic synthesis since they allow apparently impossible reactions to occur efficiently; the most useful organometallics reactions are those in which the metal acts catalytically.

A catalyst is a commodity that makes a reaction go faster, without being consumed in the process.[2] A catalytic reaction is formed of several steps that form a process called a catalytic cycle. Although the catalyst can change during the catalytic cycle, it returns to its original form at the end of the cycle. Thus, only a small quantity of catalyst relative to substrate is needed and each catalyst molecule can associate in many consecutive cycles. By virtue of a catalyst, the desired product is obtained faster besides product selectivity. There are various kinds of product selectivity. The first is a chemical selectivity (chemoselectivity) that means a situation where different chemical reactions can occur, giving different products. Regioselectivity occurs when different regions of the molecule can react with the same chemical reaction, leading to different products. When the reaction gives two or more diastereomers or enantiomers, the selectivity to each of these is called diastereoselectivity and enantioselectivity, respectively.

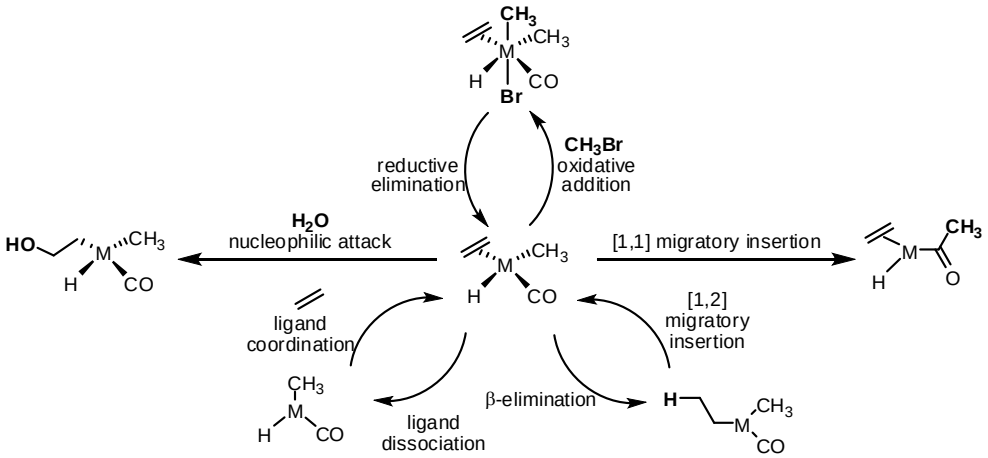
There is a variety of catalyst: Lewis acids, organometallic complexes, organic and inorganic polymers and enzymes compose the catalyst family. This big family can be divided into three categories: homogeneous catalysis, heterogeneous catalysis and biocatalysis.

Heterogeneous catalysis covers all the cases where the catalyst and the reagents, also called substrates, are in different phases while biocatalysis is the use of a natural catalyst such as enzyme to perform the chemical reaction. In homogeneous catalysis, the catalyst is in the same phase of the reactants and products. Many homogeneous catalysts are based on a transition metal that is stabilized by a ligand that is usually an organic molecule. Selecting the

[1] Elschenbroich, Ch.; Salzer, A. *Organometallics: a concise introduction* **1989,** VCH.
[2] Rothenberg, G. *Catalysis: Concepts and Green Applications* **2008** WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

right metal and the right ligand can improve the catalyst's activity, selectivity and stability. Homogeneus catalyst using organometallic complexes is an advantage in modern fine-chemicals and bulk-chemicals industry. The achievements in homogeneous chemistry is universally recognized therefore a Nobel Prize in chemistry has been awarded for the work in this area. In 2001 Prof. W. Knowles, Prof. R. Noyori and Prof. B. Sharpless shared the prize for their contribution to asymmetric hydrogenation and oxidation catalysis, respectively.[3] Four years later, Prof. Y. Chauvin, Prof. R. Grubbs and Prof. R. Schrock shared the Nobel Prize for their contribution to metathesis catalysis.[4] The last was awarded in the 2010 when Prof. R. F. Heck, Prof. E. Negishi and Prof. A. Suzuki shared the Nobel Prize in chemistry for "Palladium-catalyzed cross coupling in organic synthesis".[5] Cross coupling reactions, developed by Heck, Negishi and Suzuki, have been used for a different syntheses of natural products and biologically active compounds like Paclitaxel and Pumiliotoxin but also for the industrial preparation of fine chemicals.[6]

Every catalytic cycle is a sequence of simple chemical reactions (Scheme 1).



Scheme 1. The main elementary steps in homogeneous catalyst.

No effort is required to understand these elementary steps in homogeneous catalyst than in heterogeneous catalyst and biocatalysis because of the molecular nature of the catalyst. Elementary steps act for the building blocks which construct the reaction mechanism. We divide the elementary steps into six main categories (Scheme 1): dissociation and

[3] a) Knowles, W.S. "Asymmetric hydrogenations" (Nobel Lecture) *Angew. Chem. Int. Ed*. **2002**, *41*, 1998. b) Noyori, R. "Asymmetric catalysis: science and opportunities" (Nobel Lecture) *Angew. Chem. Int.* **2002**, *41*, 2008. c) Sharpless, K.B. "Searching for new reactivity" (Nobel Lecture). *Angew. Chem. Int. Ed.*, **2002**, *41*, 2024.

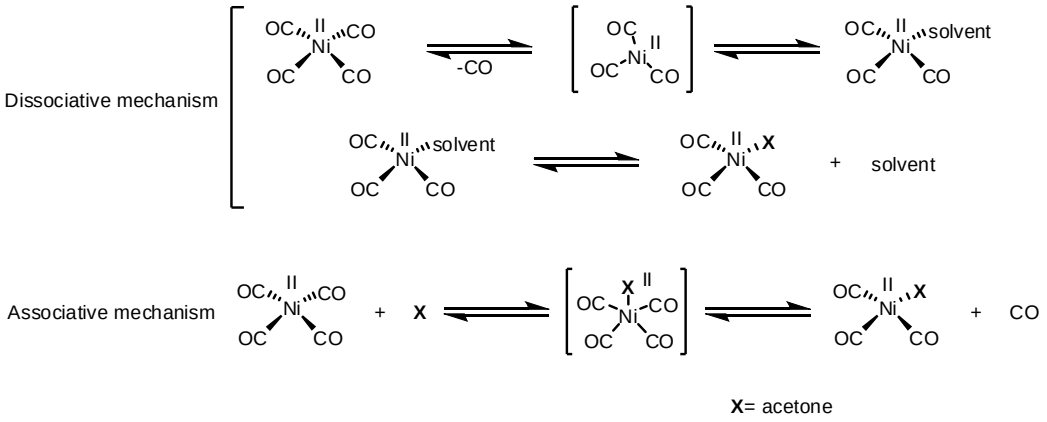
[4] a) Chauvin, Y. "Olefin metathesis: the early days" (Nobel Lecture) *Angew. Chem. Int. Ed.*, **2006**, *45*, 3740. b) Grubbs, R.H. "Olefin-metathesis catalysts for the preparation of molecules and materials" (Nobel Lecture) *Angew. Chem. Int. Ed.*, **2006**, *45*, 3760. c) Schrock, R.R. "Multiple metal–carbon bonds for catalytic metathesis reactions" (Nobel Lecture) *Angew. Chem. Int. Ed.*, **2006**, *45*, 3748.

[5] Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.*, **2012**, *51*, 5062.

[6] a) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. b) Hirashima, S.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1999**, *121*, 9873. c) Schrock, A. K. U.S. Patent US4812588, 1989. d) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8634.

coordination, oxidative addition, reductive elimination, insertion and migration, de-insertion and β-elimination and nucleophilic attack on coordinated substrate.

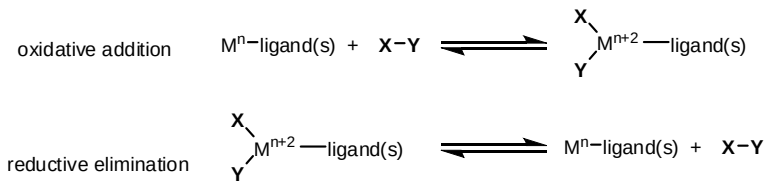
The catalyst must have a vacant site where at least one of the substrates must coordinate to allow the catalysis. In the homogenous metal complex catalyst, the vacant coordination site is at the metal atom. It is possible to have two situations that are similar to S_N1 and S_N2 nucleophilic substitution mechanisms. An example used in the reaction of the $Ni(CO)_4$ complex with acetone in THF (Scheme 2)



Scheme 2. Dissociative and associative ligand exchange from $Ni(CO)_4$.

In the first path, known as a dissociative mechanism, a CO ligand dissociates from a complex, leaving a vacant position that is filled by a solvent molecule. Thereupon, the solvent is replaced by an acetone molecule (Scheme 2, top). Dissociative mechanisms are common for six-coordinate 18-electron species like $Cr(CO)_6$. In the second case, named associative mechanism, a five-coordinated complex is arranged by the coordination of the acetone molecule to the Ni atom (Scheme 2, bottom).

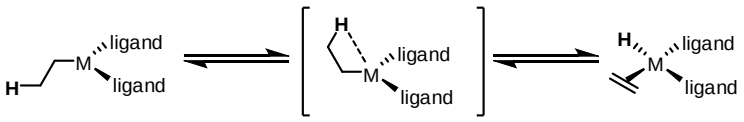
Oxidative addition is the key step in many catalytic cycles. During the reaction, a metal implants into a covalent bond X–Y that is broken and two new bonds M–X and M–Y is set up. While in the reductive elimination the bond X–Y is created from the broken of M–X and M–Y bonds (Scheme 3, top). Formally speaking, this step is deemed the opposite of oxidative addition indeed the metal loses two ligands and gains two valence electrons that metal might lose in the oxidation addition step (Scheme 3, bottom).



Scheme 3. Generic scheme for oxidative addition and reductive elimination.

Another example of bond-forming step, different from reductive elimination, is an insertion or migration step (Scheme 4). It occurs when an unsaturated ligand places in another metal-ligand bond on the same complex. De-insertion is the contrary step of insertion. The β-hydride elimination is a special case of de-insertion step in which the deserting group is an

alkene. At the end of the step a new M-H bond is given thank to a hydride abstracted from a β-carbon (Scheme 4).



Scheme 4. Generic scheme for β-hydride elimination.

The ultimate step, that we describe, is a nucleophilic attack on a coordinated substrate. When a molecule is coordinated to a metal center its electronic properties can change and a nucleophile can take place on a substrate. In many case the coordinating molecule provides electrons to the metal center, that can be positively charged, hence the nucleophilic attack on the coordinated molecule is more common.

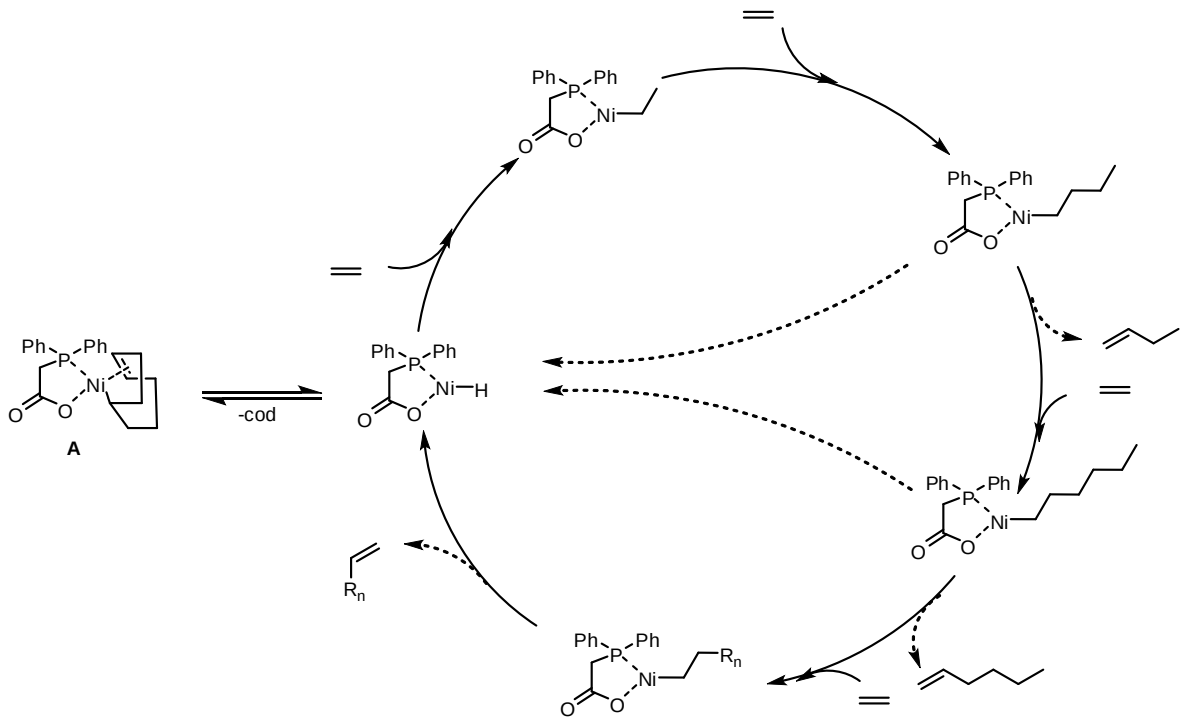
The catalytic activity is closely related to the metal and its immediate environment as the choice of ligand and the solvent. Overall, the structure/activity effects can be divided into two categories: steric effects and electronic effects. The main steric factors are: size ligand, flexibility and symmetry. The space around the metal is limited, for this reason if the ligand(s) occupy too much space, the substrate cannot coordinate and the reaction does not occurs. Hence, the ligand size is very important. Ligand dissociation frees part of the space around the metal, creating a reaction pocket which size depends on the dimension of the remaining ligands. Tolman's cone angle (θ), proposed in the 1970s, is a general measure for the size of phosphorus ligand.[7] The cone is devised, encompassing the ligand, with metal center in its apex and the P atom place in a fix length away from metal. Cone angle values typically goes from 87° for L= PH_3 up to 212° for L= P(mesityl)$_3$. Any species that coordinates to the metal center can change the electron density of the metal by pushing or pulling electrons. Tolman estimated the electronic effects of phosphorus ligands by measuring the symmetric stretching vibration frequency of the corresponding M(L)(CO)$_{n-1}$ complexes.[8] The nature of the ligand, σ-donor or π-acceptor influences the stretching vibration to the C–O *trans* to the ligand L. A strong σ-donor ligand will increase the electron density on metal center which give more back-donation to the C–O antibonding π* orbital, weakening the C–O bond and shifting the C–O stretch to longer wavelengths. The electron density will be decreased by a strong π-acceptor ligand, resulting in less back donation to the C–O antibonding π* orbital and shifting the C–O strength to lower wavelengths. Thus, the electronic effects of phosphorus ligands can be compared, using the C–O bond stretch frequencies, provide the comparison in made for a particular metal.

The catalyst efficiency is closely related to substrate/catalyst ratio but the catalyst turnover number (TON) and the turnover frequency (TOF) give a real quantity used for comparing catalyst efficiency. In homogeneous catalysis, the TON is the number of cycles that a catalyst make before it deactivates. The TOF is simply TON/time, for example the number of A

[7] Tolman, C.A. *Chem. Rev*. **1977**, *77*, 313.
[8] Tolman, C.A. *J. Am. Chem. Soc.* **1970**, *92*, 2953.

molecule can convert into B molecule with one molecule of catalyst in one second, minute or hour.

An increased number of industrial processes uses homogeneous catalyst. We report some examples of homogeneous catalysis used for a cleaner, simpler and safer processes which demonstrate the real utility of homogeneous catalysis in combination with organometallic transition metal complex. The Shell higher olefins process (SHOP) is a reaction in which the ethene is oligomerized to medium-long-chain α-olefins.[9] Based on the length of the chain, the scope of products is different as monomers (C_4-C_{10}), plasticizers (C_6-C_{10}) and biodegradable detergents (C_{12}-C_{20}) and the SHOP process can be changed on the market demands because it produces a controlled distribution of α-olefins. The oligomerization process is catalyzed by a nickel-phosfine complex. In the first step a nickel hydride complex, active catalyst intermediate, is formed from a precursor. (A, Scheme 5)



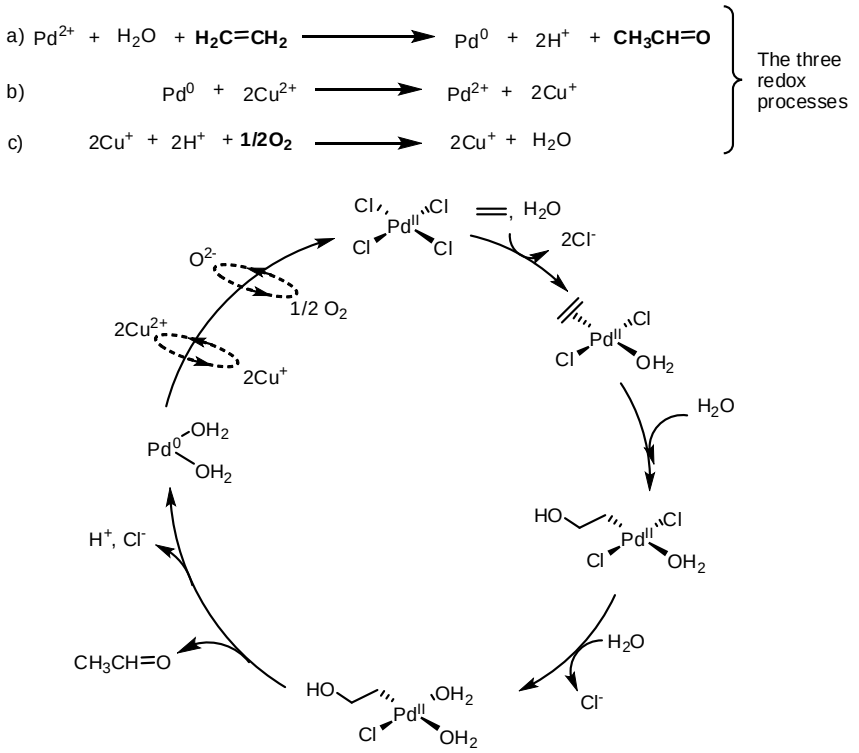
Scheme 5. Simplified catalytic cycle for the SHOP oligomerization step (the reverse reaction arrows are omitted, for clarity)

Each sequence steps of ethene insertions and β-elimination give an oligomer of a different length and regenerate the original nickel hydride complex. In addition, the overall process combines also isomerization and metathesis steps.

The Wacker oxidation process, for oxidizing olefins to carbonyl compounds, is landmark example for demonstrating the concept of catalyst regeneration with a dual-catalyst cycles promoted by a homogeneous transition metal catalysts. This process became increasingly important as it provided a simple route to acetaldehyde, starting from ethylene. The Wacker process has three main steps. In the first step, ethene reacts with a Pd(II) salt and water to give

[9] a) Lutz, E.F. *J. Chem. Educ.* **1986**, *63*, 202. b) Keim, W. *New J. Chem.* **1987**, *11*, 531. c) Keim, W. *New J. Chem.* **1994**, *18*, 93. d) Peuckert, M.; Keim, W. *Organometallics* **1983**, 2, 594.

acetaldehyde, Pd(0) and two proton. In the second step, Cu(II) re-oxidizes Pd(0) to Pd(II). Finally, the Cu(I) is re-oxidized by oxygen under acidic conditions, giving one equivalent of water and the regenerated Cu(II) salt. The catalytic cycle initiates from $[Pd(II)Cl_4]^{2-}$, as catalyst precursor, then two chlorides are replaced by a one molecule of water and ethene. The new coordinated ethene undergoes a nucleophilic attack of water followed by exchange of another chloride ligand for water and a β-hydride abstraction and coordination of the vinyl alcohol. The vinyl group then inserts into the Pd–H bond and the product is eliminated from the complex, giving a $Pd(0)(H_2O)_2$ species.[10](Scheme 6)



Scheme 6.Three stoichiometric redox reactions and simplified schematic of the palladium Wacker catalytic cycle for oxidizing to acetaldehyde.

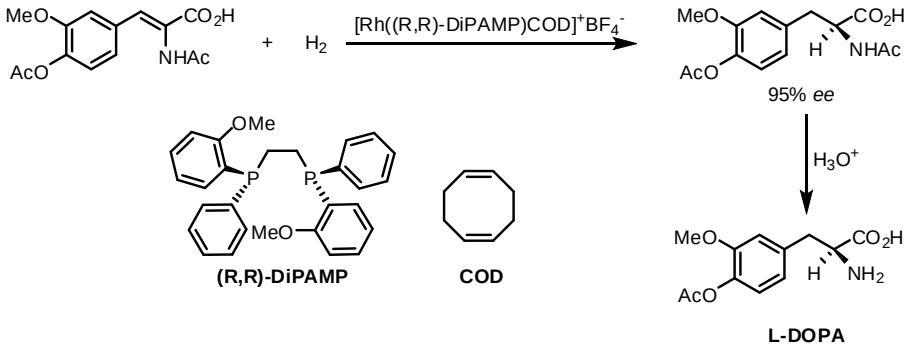
Another important and one of the largest industrial processes involving homogeneous catalyst is a synthesis of adiponitrile. Hexane dinitrile is made via double hydrocynation of butadiene catalyzed by a nickel complex.[11] Adiponitrile have an industrial important because it is a key intermediate in the manufacture of nylon 6,6 one of the most useful polyamide (annual production of 6,6 polyamide in the word is 3.4 million tonnes).

Finally, to comprehend the power of the organometallic chemistry in homogeneous catalysis, some examples of homogeneous catalyst in the synthesis of enantiomerically pure products have been reported. Indeed, most natural products are chiral and in many cases different enantiomers show different properties and can cause different effects *in vivo*. In homogeneous catalysis the use of chiral catalyst complex, where the chirality comes from the ligands,

[10] a) Moiseev, I.I.; Levanda, O.G.; Vargaftik, M.N. *J. Am. Chem. Soc*. **1974**, *96*,1003. b) The product elimination is still not clear.

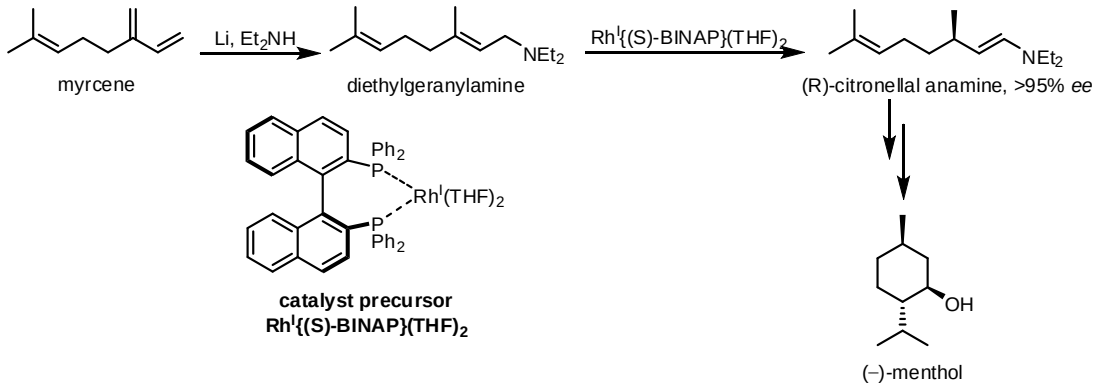
[11] a) Tolman, C.A. *J. Chem. Educ.* **1986**, *63*, 199. b) McKinney, R.J. *Organometallics* **1985**, *4*, 1142.

directs the reaction preferentially on one enantiomer over the other. One example is the use of bidentate chiral phosphane (R,R)-DiPAMP for the asymmetric hydrogenation of enamide, which yields L-DOPA (3,4-dihydroxy-L-phenylanine) with 95% *ee* (Scheme 7).[12]



Scheme 7. The synthesis of L-DOPA by using catalytic asymmetric hydrogenation.

The chiral hydrogenation product crystallized out of the reaction mixture, leaving the catalyst (substrate/catalyst ratios used is as high as 20000:1) with the remaining reactant in the mother liquor. L-DOPA, a relatively rare amino acid, is a prodrug for treating Parkinson's disease and became the first large-scale pharmaceutical manufactured by asymmetric homogeneous catalysis. In the same period Prof. R. Noyori developed the BINAP asymmetric hydrogenation catalyst that now is used also for the synthesis of (–)-menthol, an important additive for flavor, fragrances and pharmaceuticals. The key step of the synthesis, that is started from myrcene, is the isomerization of geranyldiethylamine to (R)-citronellal enamine, which is the hydrolyzed to (R)-citronellal with nearly 99% *ee* (Scheme 8).[13]

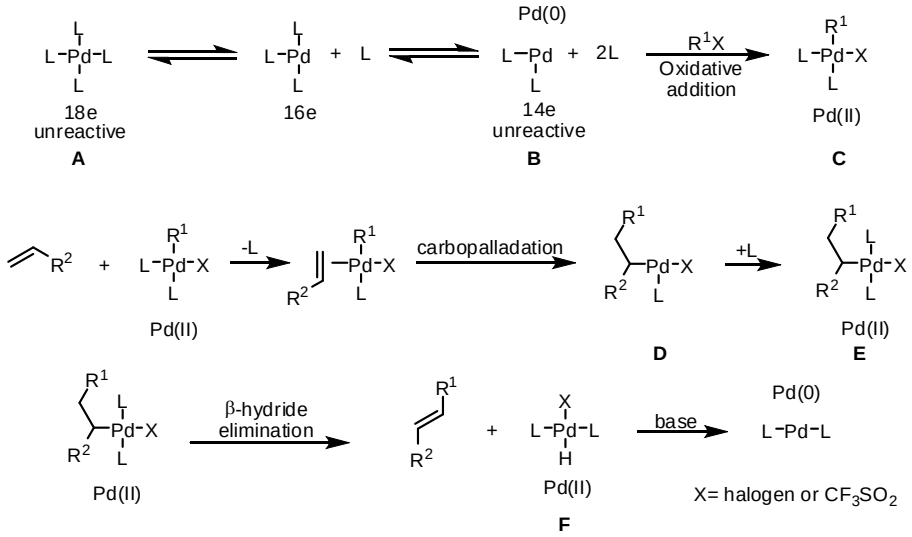


Scheme 8. (S)-BINAP-Rh complex catalyzes the asymmetric isomerization step in the synthesis of (–)-menthol from myrcene.

[12] Knowles, W. S. *Acc. Chem. Res*. **1983**, *16*, 106.
[13] a) Takaya, H., Mashima, K., Koyano, K., Yagi, M., Kumobayashi, H., Taketomi, T., Akutagawa, S., Noyori, R. *J. Org. Chem*. **1986**, *51*, 629. b) Masashi, Y., Noyori, R. *Organometallics* **1992**, *11*, 3167.

3.2 The basic Chemistry of Organopalladium Compounds

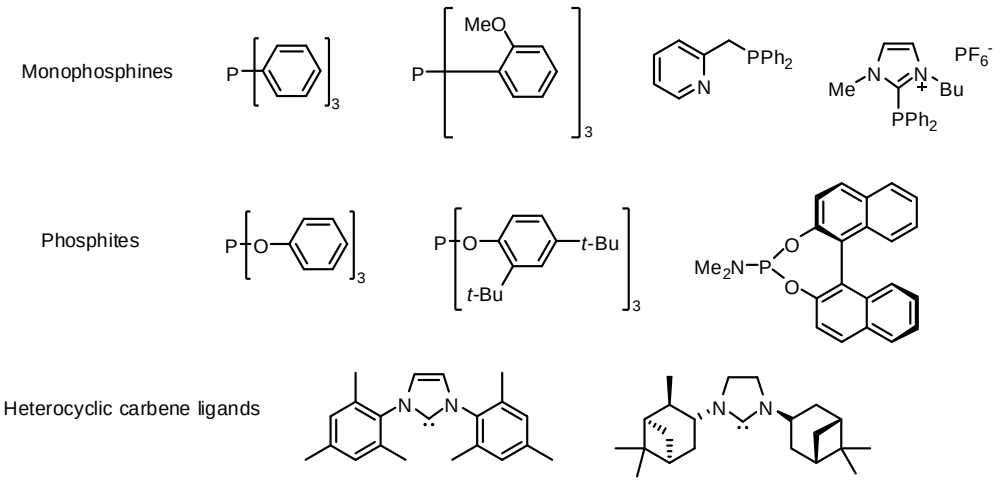
Palladium is a chemical element belonging to the 10th group of the periodic table and together with platinum, rhodium, ruthenium, iridium and osmium form a group of elements referred to as the platinum group metals (PGMs).[14] Palladium is a lustrous silver-white metal with a face-centered cubic crystalline structure; at ordinary temperatures it is strongly resistant to corrosion in air and to the action of acids. It was discovered by W. H. Wollaston in 1803 and the name derive from Pallas: the Greek goddess of wisdom, name used for the asteroid discovered one year before the chemical element. The most remarkable property of metallic palladium is its ability to absorb hydrogen, greater than for any other metal (up to 900 times its own volume). The absorption is reversible and highly selective for H_2 and D_2.
Common oxidation state for Palladium is 0, +2, + 4 while other oxidation states are currently rare. The lower, palladium (0) (Scheme 9, A) is nominally electron-rich and will undergo oxidative addition with suitable substrate, giving a palladium (II) complex. Oxidative addition is thought to occur on the coordinatively unsaturated 14-electron species (Scheme 9, B), formed by ligand dissociation in solution. The resulting Pd–R σ-bond (Scheme 9, C) in such complexes is very reactive, especially towards carbon-carbon π bonds. Thus, an alkene will lead to coordination followed by migratory insertion into the palladium-carbon σ-bond (Scheme 9, D). There is no change in oxidation state during this process, although the ligands must dissociate to allow coordination of the alkene and associative to provide a stable final 16-electron product (Scheme 9, E). Then the metal is expelled from the molecule by a β-hydride elimination and the product is an alkene plus a Pd(II) complex (Scheme 9, F). The Pd(II) product of β-hydride elimination is converted to a Pd(0) to make a process catalytic. (Scheme 9)



Scheme 9. Simplified basic reactions of palladium.

[14] a) Tsuji, J. *Palladium Reagents and catalysts: new Perspectives for the 21st Century* **2004**, John Wiley & Sons, Ltd., IBS 0-470-85032-9. b) Albéniz, A. C.; Espinet, P. *Palladium: Inorganic & Coordination Chemistry Encyclopedia of Inorganic Chemistry*, **2006**, John Wiley & Sons, Ltd.

Palladium(0) (d^{10}) form [PdL_n] complexes with phosphines, arsine, phosphites, cyanide, isocyanides and olefins. Carbon monoxide can stabilize Pd(0) in presence with σ-donor coligands in the complex, like [$Pd(CO)(PPh_3)_3$]. The high ionization energy of Pd, 805 kJ mol^{-1}, suggests that the metal would be reluctant to π-back-donate to the acceptor ligand in the absence of significant σ donation. Pure σ-donor such as amines or σ-, π-donors like halides can also stabilize Pd(0) if combined with π-acid ligands, like olefins or phosphines.[15] A common synthetic procedure to produce a Pd(0) species is the reduction of a Pd(II) compound or complex in the presence of an excess of ligands. Palladium (0) complexes are prone to undergo ligand dissociation as it already noted. The lability of the ligands in [PdL_n] complex can be used in the synthesis of mixed ligand complexes. Another easy process that occur on the coordinatively unsaturated species [PdL_n] with a various substrates giving palladium(II) complexes is the oxidative addition. Some of the formally dicoordinated [PdL_2] complexes with electron-rich bulky ligands phosphines undergo easy oxidative addition reaction by RX reagents that do not work on conventional [PdL_4] complexes. $Pd(PPh_3)_4$, one of a commercially available source of Pd(0), is a light sensitive, unstable in air, yellowish green crystal and coordinatively saturated. A number of phosphine ligand are used, among them PPh_3 is by far the most widely used, while bulky tri(*o*-tolyl)phosphine is an especially effective ligand and was used by Prof. R. F. Heck in 1978 [16] (Scheme 10)



Scheme 10. Examples of useful ligands for Palladium.

The Pd complex with tri(*o*-tolyl)phosphine is active and shows a longer catalytic life because an air and moisture stable palladacycle is formed, called Herrmann complex.[17] More electron rich phosphines like P(*n*-Bu)$_3$, tri(2,4,6-trimethoxyphenyl)phosphine and tri(2,6-dimethoxyphenyl)phosphine accelerate the oxidative addition step. In addition, P(*t*-Bu)$_3$ is a very bulky and strongly electron-donating ligand that accelerates the oxidative addition step of aryl chlorides because of the nucleophilic nature of the oxidative addition while the ligand bulkiness assists facile reductive elimination (Scheme 10, top). Phosphites, such as

[15] Kluwer, A. M.; Elsevier, C. J.; M. Bühl, Lutz, M.; Spek, A. L. *Angew. Chem. Int. Ed.*, **2003**, *42*, 3501.
[16] Ziegler, C. B.; Heck, R. F. *J. Org. Chem.*, **1978**, *43*, 2941.
[17] Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed.* **1995**, *34*, 1844.

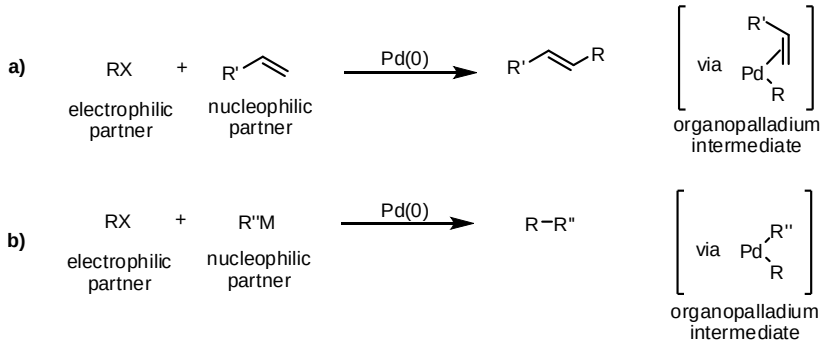
triisopropyl phosphite and triphenyl phosphite, are weaker electron donors than the corresponding phosphines, but there are used in some reactions because of their greater π-acceptor ability (Scheme 10, center).[18] The cyclic phosphites, easy to prepare not commercially available, have a small cone angle and small steric hindrance and show high catalytic activity. Heterocyclic carbenes are good ligands of transition metal complexes, called phosphine mimics, which are bulky, electron-rich and active for the reactions of aryl chlorides (Scheme 10, bottom).[19]

Pd(II) is a d^8 transition metal center. The four-coordinated square-planar geometry is energetically the most favorable, considering the splitting of the d orbitals in the Crystal Fields of different symmetry. Furthermore, Palladium (II) is a soft metallic center and can form a stable complexes with soft donor species like S-, N-, P- based ligand also it has a good affinity for the heavier halogens. Complexes containing monodentate O-donor ligands are less common only complexes with bidentate O-donors are being studied due to the chelate effect. This effect describes the enhanced affinity of chelating ligands for a metal ion compared to the affinity of a collection of similar monodentate ligands for the same metal. The main general types of derivatives with bidentate ligands can be divided into four categories (representing as X a monoanionic donor and L as a neutral donor). The first family can be outlined as $[Pd(X–X)_2]^{2-}$ where X–X is like oxalate, malonate or dithiooxalate. The second one is $[Pd(X–L)_2]$ where X–L depicts β-diketonate, glycinate-N,O-, salicylaldiminate, thioether-thiolate and dithiocarbonate. The last two families are $[PdX_2(L–L)_2]$ and $[Pd(L–L)_2]^{2+}$ in which L–L is bidentate ammine, α-diimine, 2,2'bipy, phen and bidentate phosphine.[14b]

Many of their palladium complexes are useful in catalytic process such the polymerization of olefins and others.[20] Pd-catalyzed reactions are widely used in both industrial and academic laboratories, on both minute and very large scale. The variety of reactions that can be catalyzed by Pd together with the range of functional groups tolerated and the excellent chemo- and regioselectivity.

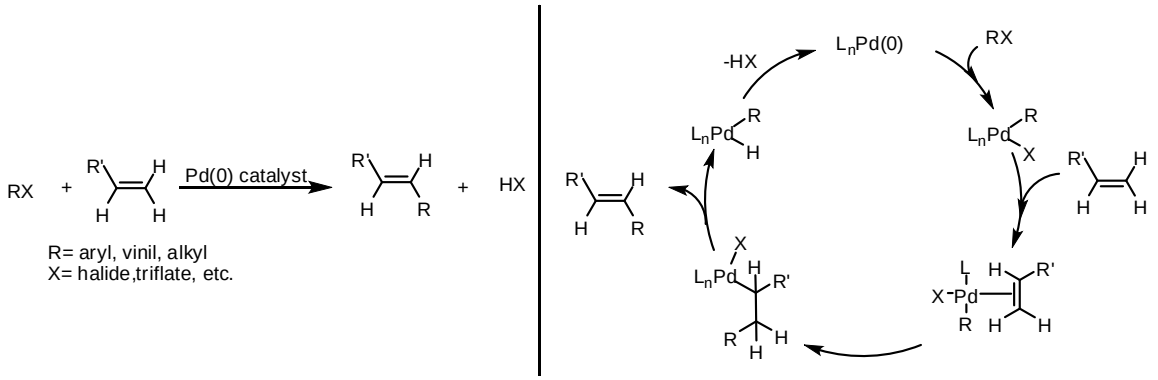
Subsequently, we allow the use of palladium chemistry in one of the key steps in the most of the synthesis of organic molecule of any complexity. The palladium-catalyzed cross coupling reactions are efficient pathway for the formation of carbon-carbon single bond. Two molecule are assembled on the metal via the formation of metal–carbon bonds. There are two types of cross coupling reactions both are catalyzed by zerovalent palladium and employ an organohalide RX as a electrophilic coupling partner (Scheme 11).

[18] van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.
[19] Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.
[20] a) Ittel, S. D.; Johnson, L. K. Brookhart, M. *Chem. Rev.*, **2000**, *100*, 1169. b) Espinet, P.; Soulantica, K. *Coord. Chem. Rev.*, **1999**,*193–195*, 499.



Scheme 11.Two types of cross coupling reactions catalyzed by palladium.

However, the nucleophilic coupling partner differs in the two pathways. Indeed, in the first type (Scheme 11, a) an olefin acts like a nucleophilic partner while in the second type (Scheme 11, b) the nucleophilic species is an organometallic compound R''M. The reactions are very mild since they utilize organic halides and the olefins or organometallic compounds R''M of low reactivity, where M is typically zinc, boron or tin. In 1968 Prof. R.F. Heck reported in addition of *in situ*-generated methyl- and phenylpalladium halides to olefins at room temperature.[21] The reaction between phenylpalladium chloride and ethylene followed by elimination of palladium (0) gave styrene. Hence, he demonstrated that the reaction can be catalytic with respect to palladium by using $CuCl_2$ as a reoxidant for Pd(0) formed at the end of the reaction.[22] An important modification, known like Heck reaction, was made in 1972 when the organopalladium complex RPdX where generated from organohalide and Pd(0) in the oxidative addition step (Scheme 12).[23] Thus, with this modification the reaction of an aryl halide and an olefin in the presence of palladium catalyst contributed an arylation of an olefin.

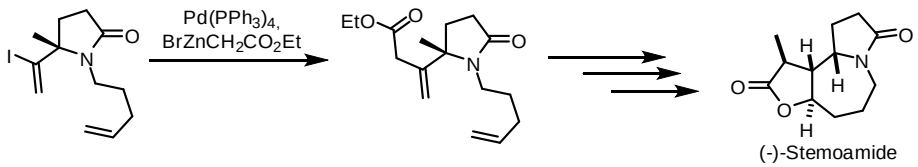


Scheme 12. Mechanism of the Heck reaction

After the formation of the organopalladium complex, the mechanism proceeds via olefin co-ordination to palladium. The olefin and the R group on palladium are assembled on the metal and can react with one another. In the next step, a migratory insertion of R group on palladium into the coordinated olefin forms a carbon-carbon bond. Finally, the β-hydride

[21] a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518. b) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5526. c) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531. d) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5542.
[22] Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5538.
[23] Heck, R. F., Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

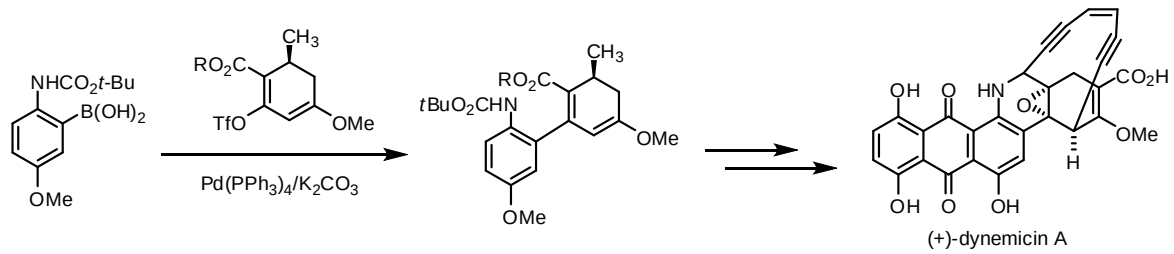
elimination forms the new olefin. In the last step a HPdX species loses HX and Pd(0) eventually is ready to enter into another catalytic cycle. The heck reaction has been used in more than 100 different syntheses of natural products and biologically active compounds like: Taxol and Morphine.[6,24] In 1976, Prof. E.-I. Neghishi started to esplore more chemoselectivite organometallics species in the palladium-catalyzed couplings with organohalides.[25] One year later organozinc compounds were introduced as the nucleophilic coupling partners in palladium-catalyzed cross coupling reaction.[26] The new methods for making carbon-carbon single bond is known as Negishi reaction. The organozinc compounds gave a product with new carbon-carbon bond in superior yields compared to other organometallic compounds and highly selectivity. Furthermore, in contrast to previous methods employing a Grignard reagent or an organolithium compound, the use of organozinc compounds allowed the coupling reaction on substrate with a wide range of functional groups (Scheme 13). [27]



Scheme 13. Negishi reaction in total synthesis of (–)-Stemoamide.

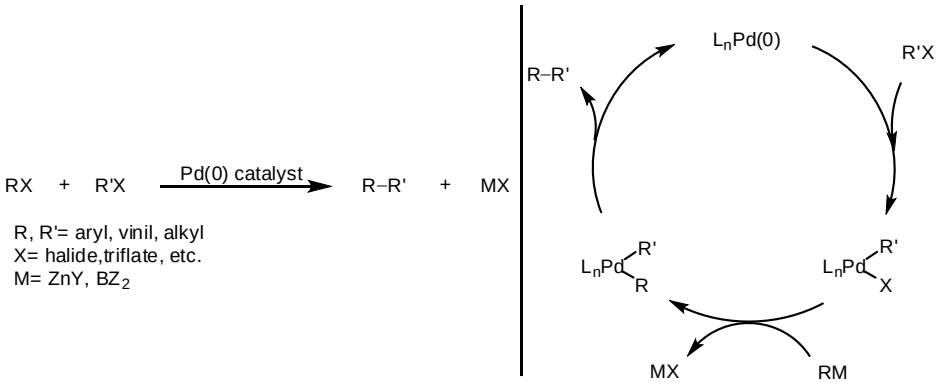
In 1976, Prof. A. Suzuki and co-workers reported the palladium-catalyzed cross coupling reactions between vinyl, aryl and alkyl halides or triflate and organoboron compounds in the presence of a base.[28] Base activation of organoboron reagents as boronate intermedias facilitate the transfer of the organic group from boron to palladium (transmetallation step). A further significant development was made using arylboronic acids as a coupling partners in the palladium-catalyzed cross-coupling reaction. In the latter case, the reaction was even more efficient and weaker bases could be employed, also organoboron compounds tolerate a wide range of functional groups under mild conditions. The reaction, called as Suzuki reaction, became very popular in the pharmaceutical industry (Scheme 14). [29]

[24] Hong, C.Y.; Kado, N., Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028.
[25] a) Negishi,E.-I.; Baba, S. *Chem.Commun*. **1976**, 596. b) Baba, S.; Negishi *J. Am. Chem. Soc.* **1976**, *98*, 6729.
[26] a) Negishi,E.-I.; King, A. O.; Okukado, N. *J. Org. Chem*. **1977**, *42*, 1821. b) King, A. O.; Okukado, N.; Negishi,E.-I. *Chem. Commun*. **1977**, 683.
[27] Torssell, S.; Wanngren, E.; Somfai, P. *J. Org. Chem*. **2007**, *72*, 4246.
[28] a) Miyaura, N.; Yamada, K. Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. b) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866.
[29] Myers, A. G.; Tom, N. J.; Fraley, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 6072-6094



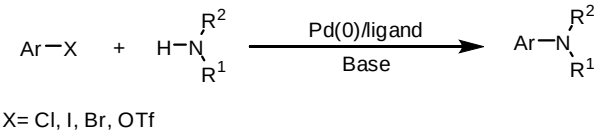
Scheme 14. Suzuki reaction in a convergent synthetic route to (+)-Dynemicin A.

The mechanisms of Negishi and Suzuki reactions start in the same way of Heck reaction: the oxidative addition of R'X to Pd(0) to give an organopalladium compound. In the second step a transmetallation occurs and the organic group R on zinc or boron is transferred to palladium. Hence, the two organic group are present on the same palladium atom via palladium-carbon bonds and in the final reductive elimination step, R' and R groups couple with one another releasing R-R' coupling product (Scheme 15).



Scheme 15. Mechanism of the Negishi and Suzuki palladium-catalyzed cross-coupling reactions.

We have seen that palladium catalyst helps form carbon-carbon bond but it can also help form carbon-hetereoatom bonds. Indeed, the Buchwald-Hartwig amination is an organic reaction used to make carbon-nitrogen bonds.[30] This is a cross-coupling reaction of an aryl halide or triflate with an amine using palladium as a catalyst with phosphine ligands and a strong base (Scheme 16). The mechanisms and catalyst used in this "Buchwald-Hartwig" chemistry mirror those of coupling reactions involving oxidative addition, transmetallation and reductive elimination.



Scheme 16. The Buchwald-Hartwig amination reaction.

[30] a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

The range of compounds which can be made is very broad: both electron-withdrawing and electron-donating substituents are acceptable. Also hindered moiety or those with acidic hydrogens such as phenol are tolerated. Aromatic heterocyclic halides work well whether they are electron-deficient or electron-rich. These reactions have been very widely used in the pharmaceutical industry. For example the synthesis of Intraconazole (Figure 1), an anti-fungal compound, uses a C-N coupling chemistry of Buchwald and Hartwig on piperazine ring with two different benzene rings to join two ends with stereochemistry.[31]

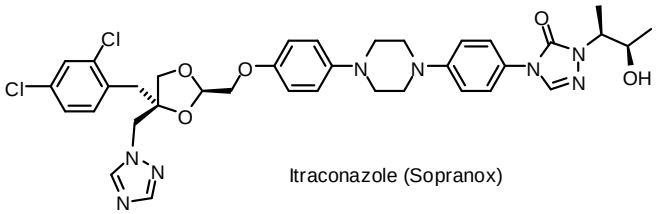
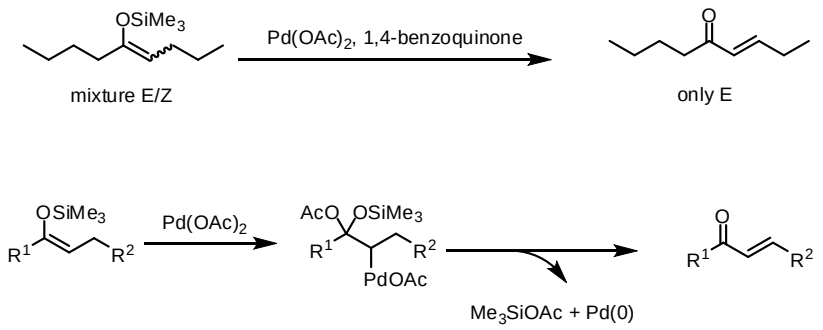


Figure 1. Chemical structure of Intraconazole.

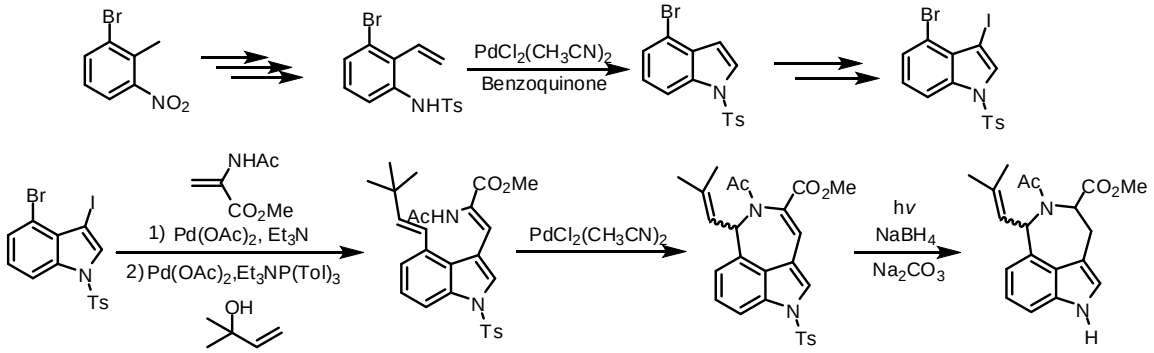
The nucleophilic attack on an isolated double bond do not occur under normal conditions. Usually alkenes react with nucleophiles only when conjugated with an electron-withdrawing group meanwhile electron-rich double bonds are poorly reactive. Despite this coordinating of an electron-rich alkene to a transition metal ion such as palladium (II) changes its reactivity dramatically. When an unsaturated ligand such as an alkene approaches the metal sideways to form a π-complex with the metal-alkene bond perpendicular to the plane of the alkene. Hence, the electron density is drawn towards the metal and away from the π orbital of the alkene and it leads to activation towards attack by nucleophiles. Many nucleophiles, such as water, alcohols and carboxylates are compatible with an alkene-Pd(II) complex and can attack the complexed alkene from opposite of the palladium. The resulting Pd(II) σ-alkyl species decomposes by β-hydride elimination to reveal the substituted alkene. Reductive elimination of a proton and the leaving group leads to palladium(0). It is necessary to use an external oxidant to convert palladium to the Pd(II) and make the cycle catalytic. A perfect example of these steps is the oxidation of terminal vinyl group to methyl ketones known as the Wacker oxidation (Scheme 6), represented in the previous paragraph. The nucleophile is simply water, which attacks the activated alkene at the more substituted end in an oxypalladatium step. β-Hydride elimination from the resulting σ-alkyl palladium complex releases the enol, which is rapidly converted into the more stable keto-form. A related reaction is the oxidation of silyl enol ethers to enones with palladium(II) acetate and 1,4-benzoquinone as a oxidant.[32] The reaction is known as Saegusa-Ito oxidation. In a recent publication a development of a new Saegusa−Ito reaction using Oxone as the stoichiometric oxidant is reported, providing a useful process for α,β-unsaturated ketone synthesis.[33] The first step of the mechanism is again oxypalladation followed by a β elimination that puts the alkene in conjugation with the ketone (Scheme 17).

[31] Hepperle, M.; Eckert, J.; Gala, D.; Shen, L.; Evans, A. C.; Goodman, A. *Tetrahedron Lett.* **2002**, *43*, 3359.
[32] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
[33] Lu, Y.; Nguyen, P. L.; Levaray, N.; Lebel, H. *J. Org. Chem.* **2013**, *78*, 776.



Scheme 17. Example of Saegusa-Ito oxidation and two simplified steps of mechanism.

Moving away from palladium by presenting a synthesis of an alkaloid, *N*-acetyl clavicipitic acid methyl ester, reported by Prof. L. S. Hegedus. The power of organometallic chemistry is illustrated in six of the twelve-step process.[34] The overall yield is 18% a remarkably good result for a molecule of such complexity. During the synthesis, an indole is made by Pd(II)-catalyzed cyclization in the presence of benzoquinone as reoxidant. Then aryl iodide are more reactive towards oxidation addition than aryl bromide and two side chains are added with two selective Heck coupling reactions. Cyclization of the amide on to the styril moiety was achieved with palladium catalysis to produce the seven-membered ring. Finally, the conjugated double bond was reduced and the sulfonamide removed under photolytic condition (Scheme 18).



Scheme 18. Total synthesis of a natural alkaloid.

3.3 Carbon Monoxide and Carbonylation Reactions

The term carbonylation reaction refers to a group of reactions that introduce carbon monoxide into organic and inorganic substrates. In organic chemistry, carbonylation produces compounds with C=O functional group such as aldehydes, carboxylic acid end esters.[35] The first well-defined carbonylation reaction was discovered just over fifty years ago by Otto

[34] Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335-4338.
[35] a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M.V. *Carbonylation: direct synthesis of carbonyl compounds* **1991**, Springer Science+Business Media New York. b) Beller, M. *Catalytic Carbonylation Reactions* **2006**, 18, Spriger-Verlag Berlin Heidelberg.

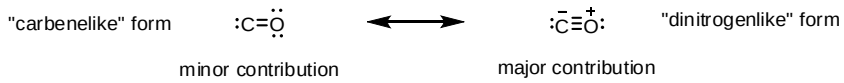
Roelen, during the mechanism studies of cobalt-catalyzed Fisher-Tropsch synthesis of hydrocarbons from carbon monoxide and hydrogen.[36] Roelen observed the formation of propanal in high yield starting from the addition of ethene to the usual feed-gas mixture of carbon monoxide and hydrogen. This reaction proved to be completely independent of the heterogeneous Fischer-Tropsch synthesis and the new process, as Roelen suggested, is catalyzed by homogeneous catalyst cobalt tetracarbonyl hydride $HCo(CO)_4$.[37] Subsequently this reaction is named hydroformylation (or oxo-reaction). It is result of the addition of hydrogen to one end of the C=C double bond and a formyl group to the other. With more than 10 million metric tons of carbonyl products per year, this reaction represents the most important use of homogeneous catalyst in the chemical industry. After Rolen's discovery, between 1939 and 1945, W. Reppe and co-workers started an extensive research program showing that many types of organic carbonyl compounds could be obtained from unsaturated hydrocarbons via stochiometric or catalytic reaction involving metal carbonyl complexes.[38] Despite some twenty-five years after the initial research about carbonylation process and many reactions types have been described, the reaction still but requires the use of high temperatures (100-300 °C), and pressure (100-1000 bar), expensive autoclave equipment, large quantities of dangerously toxic, volatile and unstable catalyst [$Ni(CO)_4$, $Fe(CO)_5$ or $HCo(CO)_4$].[39] Furthermore the reaction usually gave a complex mixture of compounds requiring separation, instead of a single major product. However, with the work of Wilkinson, Heck and Tsuji, the carbonylation chemistry dramatically changed.[40] The discovery of stable but extremely active catalyst based on organophosphine complexes of rhodium and palladium in addition with the application of new techniques, such as phase transfer, allowed many carbonylation reactions carried out at low temperature below 100°C and at pressures close to atmospheric. Moreover only very small quantities, 0.1-1 mol% non volatile, air stable catalyst precursors such as $Pd(PPh_3)_2Cl_2$ or $RhCl(CO)(PPh_3)_2$ were necessary for the process.[40] From then until today the carbonylation chemistry have grown to such an extent that it can be regarded as one of the most useful techniques of synthetic organic chemistry with a reasonably well-developed set of guidelines for choice of catalysts, reaction condition and work-up procedures.

Carbon monoxide was discovered in the 18th century by french chemist J.-M.-F de Lassone who reacted zinc oxide with coke producing CO but mistakenly he concluded that the gaseous product was hydrogen, as it burned with a blue flame. Soon after, it was first identified by W. C. Cruikshank.[41] Carbon monoxide is a colorless, odorless gas, liquefying at -191.5 °C. It is a poison gas, which enters the organism through the respiratory system. The bulk of absorbed CO (approx. 80–90%) binds with hemoglobin, and carboxyhemoglobin is the marker of CO

[36] Roelen, O. **1938** German Patent No. 849,548. (b) Herrmann, W. A. *J. Organomet. Chem.***1990**, *383*, 21.
[37] Orchin, M. *Acc. Chem. Res.* **1981**, 14, 259.
[38] Reppe, W. **1939**, German Patent No. 855,110.
[39] C. W. Bird *Chem. Rev.***1962**, 62, 283.
[40] a) Osborn, J. A.; Young, J. F.; Wilkinson, G. *J. Chem. Soc., Chem. Commun.***1965**, 17. b) Heck, R. F. *Palladium Reagents in Organic Synthesis* **1985,** Academic Press, New York. (b) Tsuji, J. *Organic Synthesis with Palladium Compounds* **1980,** Springer-Verlag, Berlin.
[41] Cruickshank, W. *Some additional observations on hydrocarbonates, and the gaseous oxide of carbon J. Natural Philos., Chem. Art* **1801**, *5*, 201−211.

action. CO is highly toxic to organisms at elevated concentrations and has about 245 times greater affinity for hemoglobin and myoglobin than oxygen. However, CO interference with oxygen transport in blood due to its binding to heme iron centers in hemoglobin is not a major contributor to CO toxicity, but rather the increase in CO tissue concentration leading to disruption of mitochondrial function.[42] It has also the ability to bind to the cytochrome oxidase and cytochrome P450, which results in inhibition of cellular respiration. Prolonged esposure to lower concentrations causes shortness of breath and headache followed when exposure is severe, to confusion, dizziness and impaired hearing and vision. Hence, an efficient fume cupboard is necessary to keep emissions in the laboratory atmosphere to an absolute minimum when it is required to work with carbon monoxide. Also under normal circumstances when working with small amounts of the gas in a efficient fume cupboard, the risk of fire and explosion is minimal because the limits of flammability in air for carbon monoxide at atmospheric pressure and room temperature are 12.5% vol (lower) and 74.2% vol (upper).[35a]

The conventional valence bond description of carbon monoxide involves two canonical forms (Scheme 19). The first one is "carbenelike" structure in which divalent carbon is linked to oxygen by a double bond. The second form, as "dinitrogenlike" is when a triple bond linked both atoms carry a lone pair. The latter canonical form, which is by far the more important, leads to the assignment of formal O (+) and C(-).



Scheme 19. Valence bond description of carbon monoxide.

This very simple description is coherent with many of the physical properties of carbon monoxide like the very high C–O bond energy (1076 kJmol^{-1}) and the short bond length (1.128 Å). Some of physical proprieties of carbon monoxide are reported in Table 1. [35a]

Table 1. Physical Properties of carbon monoxide

Melting point	-205 °C (1bar)
Boling point	0.84 kJmol-1
Density (gas)	1.25 g liter-1 (at 0°C/1 bar)
Bond length	1,128 Å
Bond energy	1076 kJmol-1
Dipole moment	1.2 x 10-2
Ionization potential	1.35MJmol-1

The triple bond characteristic, like the short carbon-oxygen bond distance and a high dissociation energy are also evident from the molecular orbital (MO) diagram (Figure 2, A). Two σ and σ* are formed by the overlap of the 2*s* atomic orbitals of carbon and oxygen, whereas the 2*p* leads three bonding and three anti-bonding MOs, a pair of σ/ σ* character and two each of π and π* character. In total four of the bonding but only one of the anti-bonding MOs are doubly occupied, resulting an exceptionally strong bond. However, the presence of

[42] Schatzschneider, U. *Br. J. Pharmacol.* **2015**, *172*, 1638.

relatively low-lying empty MOs of π* character is important for the reactivity and binding of CO to metals. The energetically highest filled orbital of carbon monoxide, which is of a σ* character, can form a σ-donor interaction thanks to the overlap with symmetry-adapted empty *d* orbitals on the transition metal center (Figure 2, B, bottom). At the same time, a π-donor interaction between the next highest occupied π orbital on the carbon monoxide with suitably oriented empty metal *d* orbitals is also present (Figure 2, B, center). In contrast, an additional π-acceptor interaction, known as backbonding, is arranged from occupied metal *d* orbitals with empty low lying MOs of the carbon monoxide (Figure 2, B, top).[42]

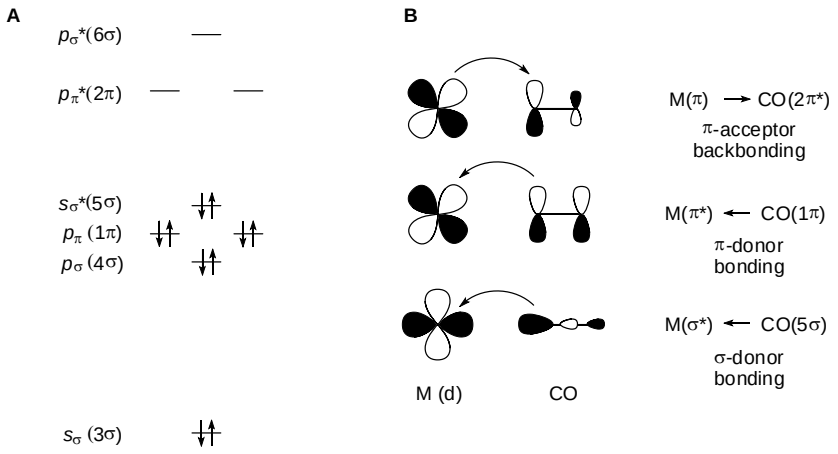
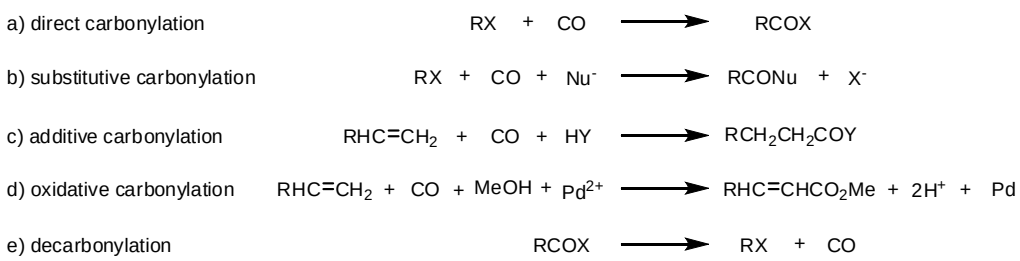


Figure 2. Molecular orbital (MO) diagram of carbon monoxide (A); bonding and backbonding interactions in transition metal-CO complexes (B).

The backbonding is among the characteristic features of the different types of metal carbonyl complexes and their stability of this type of compound. Therefore, a transition metal centers in relatively low oxidation states preferentially form carbonyl complexes, since the metal center with filled *d* orbitals of proper energy facilitate the backbonding. Furthermore, the presence on electron-donating or withdrawing ligands on the metal center can modulate the strength of the M-(CO) bond. A decrease in the metal *d* electron density will result in subsequent weakening of the backbonding and thus facilitate CO release from the metal coordination sphere. This can be achieved, for example, by chemical or electrochemical oxidation of a low-valent metal centre.

The chemistry of coordinated carbon monoxide compounds is quite the same of the transition organometallics compounds, and the elementary reactions in organo-transition metal chemistry such as oxidative addition, nucleophilic attack and reductive elimination can occur. The most characteristic reaction of coordinated carbon monoxide is the insertion process in which a carbonyl ligand undergoes concerted intramolecular attack by another ligand, typically an alkyl, aryl or other 1-electron ligand. The importance of the insertion in CO-based synthetic organic chemistry can scarcely be overemphasized since nearly all catalytic carbonylation reactions, and many stoichiometric syntheses, rely on insertion of carbon monoxide.

The carbonylation chemistry is a very extensive topic in chemistry and the different types of reactions can be rationalized in some elementary reactions (Scheme 20).[35a]



Scheme 20. Classification of different types of carbonylation reaction.

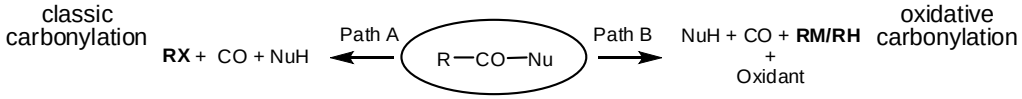
The first simplest of all carbonylation reactions is the direct carbonylation. The best example for this category is the conversion of iodomethane to acetyl iodide through the oxidative addition to the Rh(I) complex, followed by methyl migration to a carbonyl ligand and reductive elimination of acetyl iodide (Scheme 20, a).[43] Direct carbonylation of an organic halide is a rather rare synthetic process and system in which halide ion is replaced by a nucleophile during the reaction are much more frequently encountered (Scheme 20, b). This is a particularly versatile type of reaction, named as substitutive carbonylation, in that it provides a wide range of carbonyl anion equivalents ($[NuCO]^-$) allowing the synthesis of many carboxylic acid derivatives directly from organic halides. As an example, bromoarene is carbonylated by palladium-catalyst and after the reductive cleavage occurs by whichever nuclephile (MeOH, H_2O ecc.). Additive carbonylation occurs when hydrogen is added to one end of the C=C double bond and a formyl group to the other (Scheme 20, c). Hydroformylation reaction belong to this class of reaction. Replacing hydrogen in this synthesis with water, the reaction yields carboxylic acid (hydrocarboxylation), with an alcohol yields esters (hydroesterification). The general mechanism pattern of these reactions is very similar although different catalysts may be required. Carbonylation reactions, in which the transition metal undergoes a reduction during the carbonylation of the substrate is known as oxidative carbonylation (Scheme 20, d). In order to achieve a catalytic reaction, it is necessary to use an oxidant to reoxide the metal, back to the active species. The carbonylation reactions may be reversible and the metal complexes that catalyze carbonylation of organic compounds should also might catalyze their decarbonylation (Scheme 20, e) [44]. The key step is the fragmentation of the acyl ligand to give an alkyl or aryl moiety and coordinated carbon monoxide. As an example, the complete cycle for catalytic decarbonylation of an aldehyde by $RhCl(CO)(PPh_3)_2$.

3.4 Oxidative Carbonylation

During the last few years, oxidative carbonylation have acquired a growing importance thanks to the development of new and selective catalytic systems, mainly based on palladium, which are able to form of highly functionalized carbonyl compounds in one step starting from simple

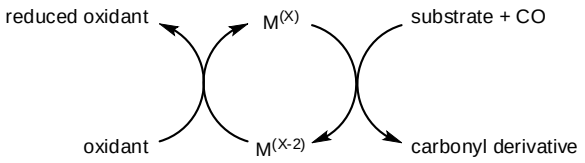
[43] Forster, D. *J. Am. Chem. Soc.***1976**, *98*, 846.
[44] D. H. Doughty, in *Homogeneous Catalysis with Metal-Phosphine Complexes* **1983** (L. H. Pignolet, ed.), p.343, Plenum, New York.

building block under mild condition.[45] In classic carbonylation an organohalides, which act as a electrophiles, is converted into the corresponding carbonylated product thanks to the presence of a Pd(0) catalyst (Scheme 21, path A).[46] Harsh conditions such as high temperature and high pressure of CO is generally required, because carbon monoxide as a π-acceptor makes the low-valent catalyst electron deficient, thus the oxidative addition of organohalides towards Pd(0) species do not occurs easily.[47] On the other hand, oxidative carbonylation reaction is a process in which a carbon monoxide is inserted into a substrate, such as alkenes, alkynes and organometallics, under the action of a metal catalyst, generally a Pd(II) complexes (Scheme 21, path B).



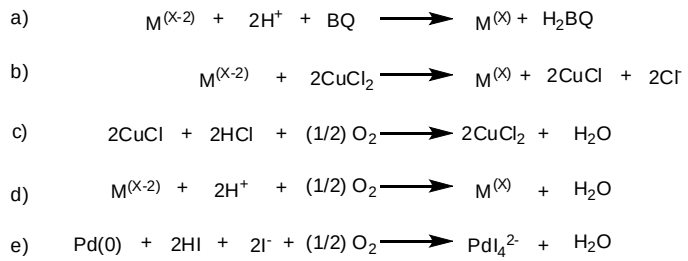
Scheme 21. Comparison of the classical carbonilation (path A) and oxidative carbonylation (path B).

The transition metal catalyst, during the oxidative carbonylation, undergoes a reduction of its oxidation state [Pd(II) to Pd(0)] and in order to achieve a catalytic reaction an esternal oxidant is required (Scheme 22).



Scheme 22. General reaction for the oxidative carbonylation.

The suited oxidant are usually organic compound or inorganic salt, such as benzoquinone (Scheme 23, a), copper(II) chloride (Scheme 23, b) or silver salt. In the case of $CuCl_2$, the resulting copper(I) chloride may be reoxidized by means of oxygen or other oxidant (Scheme 23, c). Direct oxidation with O_2 is also possible (Scheme 23, d), and it is very efficient with the presence of iodide anion to transform Pd(0) to PdI_4^- (Scheme 23, e).

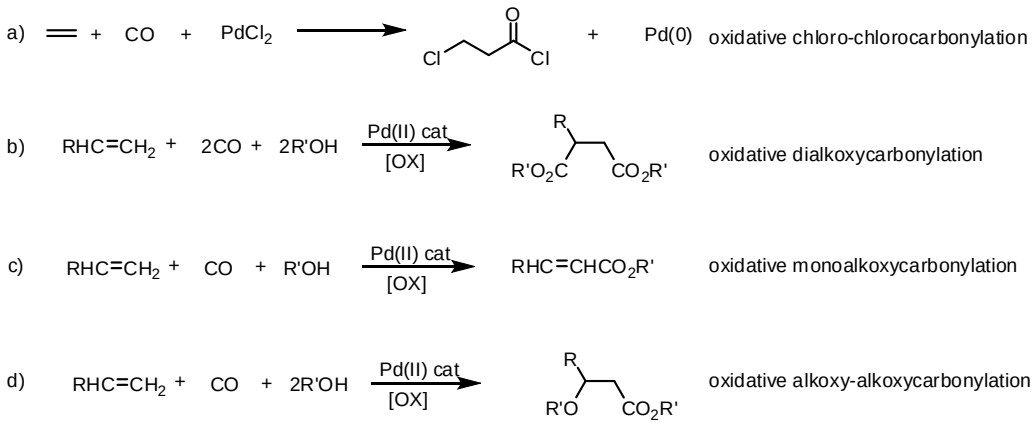


Scheme 23. Reoxidation reaction with organic and inorganic oxidant.

[45] Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Sus. Chem.* **2013**, *6*, 229.
[46] a) Heck, R. F.; Breslow, D. S.; *J. Am. Chem. Soc.* **1963**, *85*, 2779. b) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318.
[47] Zanti, G.; Peeters, D. *Eur. J. Inorg. Chem.* **2009**, 3904.

When the oxygen is used as reoxidant for Cu(I) water is formed as a co-product. Indeed, in the presence of water a competitive oxidation reaction may take place, such as oxidation of CO to CO_2, as a consequence the activity of the catalyst toward the desired carbonylation reaction is decreased. A dehydrating agent can be use to reach good catalytic efficiencies and product yields. Oxidative reaction might also proceed under milder condition and the substrates are all nucleophiles and many of which are widely available. Moreover the oxidative carbonylation on R–H compound would greatly reduce the cost of the carbonylation process because the starting material is not R–X, such as in classic carbonylation, that are normally prepared from the corresponding nucleophilic R–H.

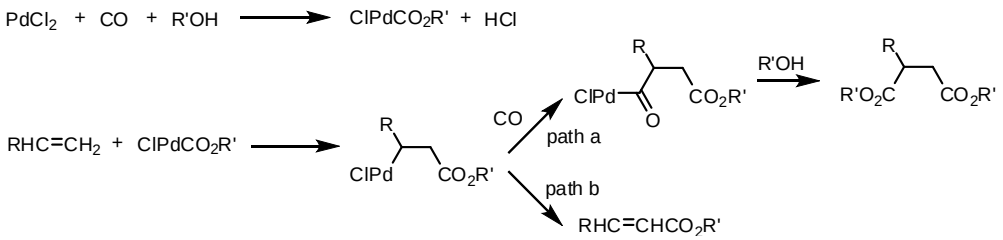
A wide range of organic substrates can be converted into a carbonyl product by using oxidative carbonylation. Alkenes can be carbonylated in a various products such as β-chloroalkanoyl, (Scheme 24, a),[48] succinic diesters (Scheme 24, b),[49] α,β-unsaturated esters (Scheme 24, c)[50] or β-alkoxyalkanoic (Scheme 24, d),[51] based on reaction conditions. All these reactions are promoted by Pd(II) species in stoichiometric amount or in catalytic fashion with the assistance of an oxidant.



Scheme 24. Examples of oxidative carbonylation on alkenes.

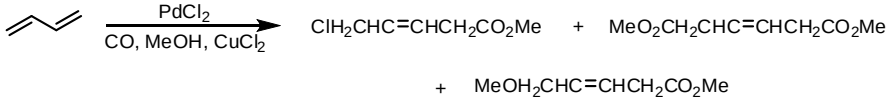
Succinic diesters and acrylic esters are formed through insertion of the olefin into the Pd–C bond of an alkoxycarbonylpalladium species $XPdCO_2R$, obtained from the reaction between PdX_2, CO and R'OH used as external nucleophile. Eventually, succinic ester is formed from the second carbon monoxide insertion, followed by nucleophilic displacement by R'OH (Scheme 25, path a) whereas the α,β-unsaturated ester may be attained as a result of β–hydrogen elimination of the carbonyl palladium (Scheme 25, path b).

[48] a) Tsuji, J.; Morokawa, M.; Kiji, M. *J. Am. Chem. Soc.* **1964**, *86*, 4851.b) Tsuji, *J. Acc. Chem. Res.* **1969**, *2*, 144.
[49] a) Yukawa, T.; Tsutsumi, S. *J. Org. Chem.* **1969**, *34*, 738. b) Yukawa, T.; Tsutsumi, S. *J. Org. Chem.* **1969**, *34*, 738.
[50] a) Cometti, G.; Chiusoli, G.; *J. Organomet. Chem.* **1979**, *181*, C14. b) Bianchini, C.; Mantovani, G.; Meli, A.; Oberhauser, W.; Brüggeller. P.; Stampfl, T. *J. Chem. Soc., Dalton. Trans.* **2001**, p 690.
[51] James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810.



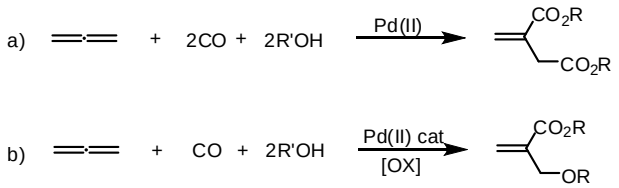
Scheme 25. Mechanism of oxidative carbonylation to lead succinic diester and α,β-unsaturated ester.

The R'OH, used as a external nucleophile, may be replaced by amines, acids or carbanion; for example when acetoxy group is an external nuleophile, the final product is a β-acyloxyanhydride.[52] Moreover when a nucleophilic function is present in the starting alkene in a suitable place for a cyclization, a formation of heterocyclic derivatives migth occur.[53] Conjugated dienes and allene can also undergo Pd-catalyzed oxidative carbonylation. In the first case 1,3-butadiene has been converted in a mixture of 1,4-addition products (Scheme 26).[54] From the $ClPdCO_2Me$ intermediate, a chloroester or methoxycarbonylation is formed by the addition to the double bond followed by reductive elimination, while the methoxyester results from MeOH attack on coordinated double bond, followed by methoxycarbonylation.



Scheme 26. Oxidative carbonylation of 1,3-butadiene.

The oxidative bis-alkoxycarbonylation with a stoichiometric amount of $PdCl_2$ (Scheme 27, a) and alkoxy-alkoxycarbonylation under catalytic condition can happen on allene substrates (Scheme 27, b).[55]



Scheme 27. Oxidative carbonylation on allenes.

Alkynes is converted into various carbonyl derivatives by means of the oxidative carbonylation reactions promoted by Pd(II) species in the presence of an oxidizing agent. The first example of oxidative carbonylation of alkyne reported was the dichlorocarbonylation of acetylene promoted by stoichiometric $PdCl_2$ (Scheme 28).[48a]

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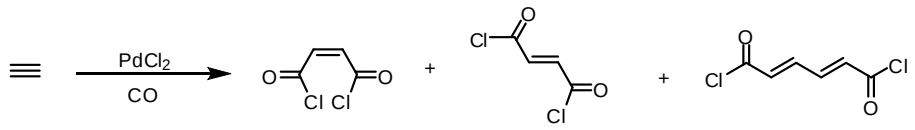
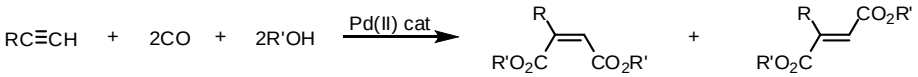
[52] Urata, H.; Fujita, A.; Fuchikami, T. *Tetrahedron Lett.* **1988**, *29*, 4435.
[53] a) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 358. b) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y.; *J. Org. Chem.* **1997**, *62*, 2113.
[54] Stille, J. K.; Divakaruni, R. J. *J. Org. Chem.* **1979**, *44*, 3474.
[55] a) Tsuji, J.; Susuki, T. *Tetrahedron Lett.* **1965**, 3027. b) Alper, H.; Hartstock, F. W.; Despeyroux, B. *J. Chem. Soc., Chem. Commun.* **1984**, 905. c) Alper, H.; Hartstock, F. W.; Despeyroux, B. *J. Mol. Catal.* **1986**, *34*, 381.



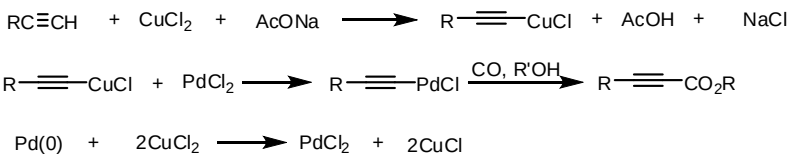
Scheme 28. First example of oxidative carbonylation of alkyne

Maleic and fumaric esters are formed by Pd(II)-catalyzed dialkoxycarbonylation of alkynes with $CuCl_2/O_2$ as oxidant system (Scheme 29). The mechanism pathway for the alkynes is closely related to the bis-alkoxycarbonylation (Scheme 25, path a).[56]

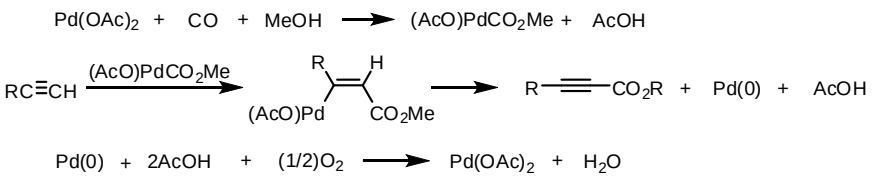


Scheme 29. Bis-alcoxycarbonylation of alkynes.

Conversaly, mono-alkoxycarbonylation of 1-alkynes to give 2-ynonate ester is a general reaction, which may occurs under basic condition, thanks to the formation of alkynylpalladium species (Scheme 30)[57] or from alkoxycarbonylvinylpalladium species (Scheme 31).[58]



Scheme 30. Mono-alkoxycarbonylation of 1-alkynes via alkynylpalladium species.

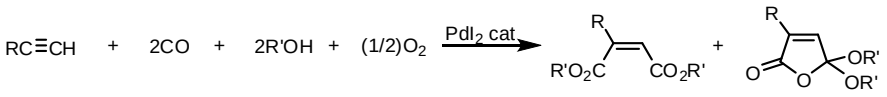


Scheme 31. Mono-alkoxycarbonylation of 1-alkynes via alkoxycarbonylvinylpalladium species.

Different kinds of oxidative carbonylation reactions on alkynes bearing a nucleophilic group in suitable position for cyclization to give a functionalized heterocyclic derivatives are possible. Both oxidative cyclocarbonylation with incorporation of CO into the cycle or oxidative cyclization-carbonylation, without incorporation of carbon monoxide into the cycle

[56] a) Chiusoli, G. P.; Venturello, C.; Merzoni, S. *J. Soc. Chem. Ind.* (London) **1968**, 977. b) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1007. c) Giannoccaro, P.; Aresta, M.; Doronzo, S.; Ferragina, C. *Appl. Organomet. Chem.* **2000**, *14*, 581.
[57] a) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* 1980, 849. b) Izawa, Y.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2033.
[58] Sakurai, Y.; Sakaguchi, S.; Ishii. Y. *Tetrahedron Lett.* **1999**, *40*, 1701.

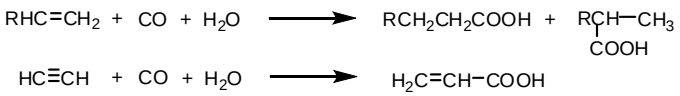
may occur using Pd(II) species as catalyst. Several alkynols and alkynamines have been successfully cyclized into β- and γ-lactones or lactams.[59]
The oxidative carbonylation on simple and functionalized alkynes has been reached with PdI_2 with an excess of iodide anions.[56 b,60] Indeed, alkyl- or arylacetylenes under mild condition in alcoholic solvent may be converted into maleic derivatives and 5,5-dialkoxyfuran-2(5*H*)-ones (Scheme 32). The furanone derivatives were easily transformed into maleic esters.[61]



Scheme 32. Oxidative oxidation of alkynes catalyzed by PdI_2/KI.

3.5 Hydro- and Alkoxycarbonylation of Alkenes and Alkynes

The use of carbon monoxide as building block in presence of water or an alcohol to functionalize unsaturated substrates by hydrocarbonylation or alkoxycarbonylation reaction to produce oxygenate compounds with high selectivity is a challenge in metal-catalyzed organic synthesis. After the early work of Reppe in 1930s,[62] reactions selectivity has been gradually improved thanks to the progress in coordination chemistry that allowed to improve the operating condition by designing the metal center and its ligand.
The reaction of hydroxycarbonylation are related to the incorporation of carbon monoxide and H_2O into alkenes or alkynes leading to the corresponding saturated or unsaturated carboxylic acid. The general equations are reported below (Scheme 33).



Scheme 33. The general equations of hydroxycarbonylation of alkenes and alkynes

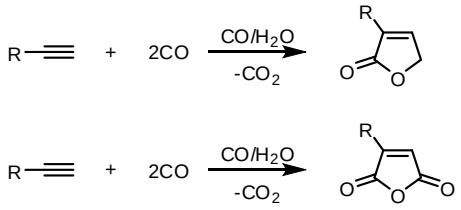
In 1969, von Kutepow and co-workers reported the hydroxycarbonylation of a terminal alkene using phosphine palladium complexes.[63] Alper and co-workers discovered that is possible to obtain a branched carboxylic acid in a selective way by adding copper (II) chloride and hydrochloride to a palladium catalyst.[64] The reaction is performed in mild condition (room temperature and at 1 bar of carbon monoxide) also the enantioselective carbonylation can be carried out by addition of a phosphate chiral ligand, reaching an enantiomeric excess as high

[59] Bonardi, A.; Costa, M.; Gabriele, B.; Salerno, G.; Chiusoli, G. P. *Tetrahedron Lett* **1995**, *36*, 7495. Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607.
[60] Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc. Perkin. Trans. 1* **1994**, 83.
[61] Gabriele, B.; Veltri, L.; Salerno, G.; Costa, M.; Chiusoli, G. P. Eur. *J. Org. Chem.* **2003**, 1722.
[62] a) Reppe, W.; Magin, A.; Schuster, C.; Keller, R.; Kroper, H.; Klein, T.; Kerchow, F. W.; Blank, G.; Merchel, K.; Scheller, H.; Weschky, L.; Wolff, K.; Schwenckendiek, W.; Hecht, W.; Gassenmeier, E.; Simon, A. *Liebigs Ann. Chem.* **1953**, 582:1.
[63] Von Kutepow, V.; Bittler, K.; Neubauer, D. US Patent, 3,437,676 , **1969**, to Badische Anilin and Soda-Fabrik.
[64] Alper, H.; Woell, J. B.; Despeyroux, B.; Smith, D. H. J. *J. Chem. Soc. Chem. Commun.*, **1983**, 1270.

as 91%.[65] Hydroxycarbonylation has been also performed in biphasic media because of the water-soluble mono- or diphosphine ligands that maintain the catalyst in aqueous phase.[66] Palladium, in the presence of the sodium salt of trisulfanated triphenylphosphine, can carbonylate efficiently acrylic ester, propene and light alkene while for heavy alkenes the presence of dimethyl-β-cyclodextrin, an inverse phase transfer agent, improved the activity of the process.[66] On the other side, high conversion and high selectivity in linear acid product is possible to reach by using palladium acetate and 1,4-bis(diphenylphosphino)butane in acid condition.[67]

The pioneering work of Reppe and co-workers was based on the industrial preparation of acryl acid by carbonylation of acetylene catalyzed by $Ni(CO)_4$ in the presence of a copper halides. The reaction was conducted at 200-230°C and 100 bar of CO.[68] Later, the hydroxycarbonylation of alkynes can be performed under mild condition in biphasic medium by using a phase transfer.[69]

It is worth mentioning that the reductive carbonylation of alkynes occurs in the presence of CO/H_2O couple. The terminal alkynes have been selectively converted, in the presence of PdI_2/KI, into furan-2-(5H)-ones or anhydrides; with a high concentration in CO_2 (Scheme 34). A cyclization, together with the formation of an oxygen-carbon bond can occur on palladium with the incorporation of two CO building blocks through a cascade reactions.[70] The main role of water is to give hydrogen through the water-gas-shift reaction, as the co-production of CO_2 demonstrates.



Scheme 34. Incorporation of two CO building-blocks into alkynes under water-gas-shift condition.

Carbonylation reaction under water-gas-shift conditions have been largely explored because of the high value of cyclic compounds that show a biological activity.

In the alkoxycarbonylation reactions, carbon monoxide and alcohol react giving esters or lactones. Alkenes or an alkynes are suited substrates for the carbonylation reaction, but it is

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[65] Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.

[66] a)Tilloy, S.; Monflier, E.; Bertoux, F.; Castanet, Y. *New. J. Chem.* ,**1977**, *21*, 529. b) Papadogiakis, G.; Verspui, G.; Maat, L.; Sheldon, R. A. *Catal. Lett.*, **1997,** *47*, 43. c) Verspui, G.; Feiken, J.; Papadogiakis, G.; Sheldon, R, A. *J Mol Catal A: Chem* **1999,** *143*, 299. d) Monflier, E.; Tilloy, S.; Bertoux, F.; Castanet, Y.; Mortreux, A. *New J Chem* **1997,** *21*, 857. e) Bertoux, F.; Monflier, E.; Castanet, Y.; Mortreux, A. *J Mol Catal A: Chem* **1999**, *143*, 11.

[67] Goedheijt, M. S. ; Reck ,J. N. H.; Kamer, P. C. J.; Van Leeuwen, P. N. M. *Chem Commun* **1998**, 2431.

[68] Weissermel, K.; Arpe, J. H. *Industrial Organic Chemistry* **1997** Third Completely Revised Edition Wiley, Weinheim, p 290.

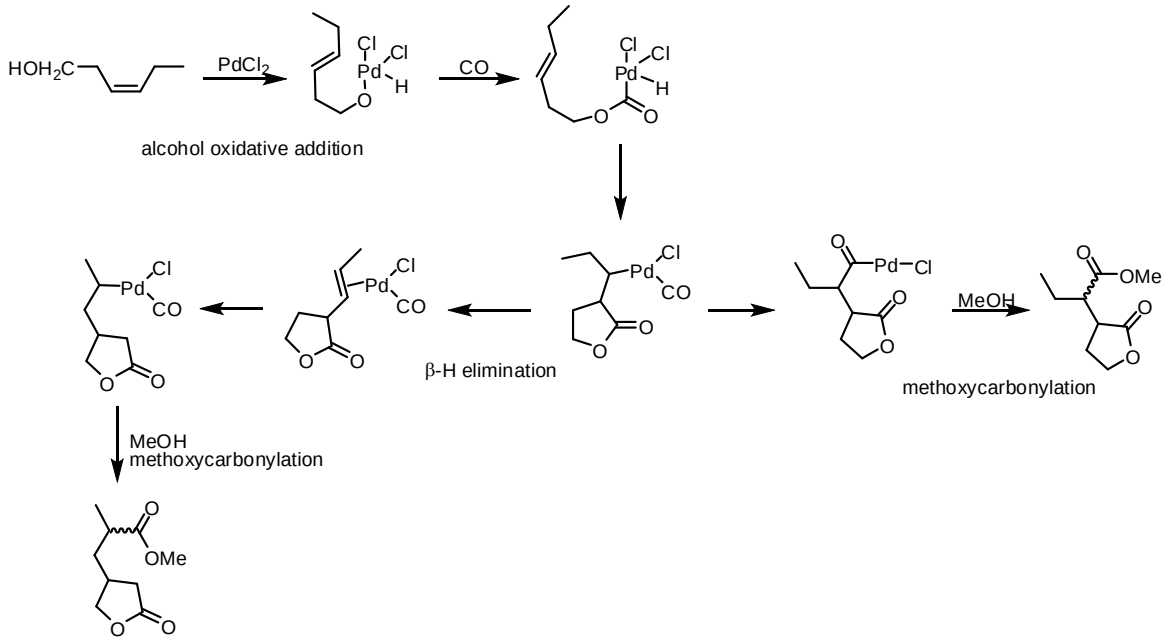
[69] Amer, I.; Alper, H. *J Organomet Chem* **1990**, *383*,573.

[70] a) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett* **1999,** *40*, 989. b) Chiusoli, G. P.; Costa, M.; Cucchia, L.; Gabriele, B.; Salerno, G.; Veltri, L. *J. Mol. Catal. A: Chem.* **2003**, *204–205*, 133

also possible to start from active halides to produce the same product. Although in the early examples high pressure were necessary for catalyst precursor, recently new generation of noble metal-base catalyst have been developed, allowing the researchers to work under milder conditions to improve yields and selectivity. Intermolecular alcoxycarbonylation of alkenes can be seen like a substitution of hydrogen atom on alkene by a carbomethoxy group. The pioneer of this field was Heck that studied the alkoxycarbonylation of ethylene catalyzed by $Pd(OAc)_2$.[71] Stille and James have discovered that the Pd source together with Cu source catalyzes the incorporation of COOMe group arose from carbon monoxide and methanol.[72] Most of reactions, with a stoichiometric quantities of copper, and alkene can produce a diester or a methoxyester. Later Inomata and co-workers reported that is possible to drive the reaction to monoester or diester based on the use of Cu(II) source or Cu(I) respectively.[73] Various terminal aliphatic alkene are converted into the corresponding monoester with a palladium complex as $[PdCl_2(PPh_3)_2]$ by indroducing of $SnCl_2$ to improve the selectivity of the carbonylation into the linear ester.[74] This procedure has been successfully applied to the alkoxycarbonylation of monoterpenes, such as limonene, leading to ester derivatives of abundant natural products, with potential application in perfumery, flavor and pharmaceutical industries.[75]

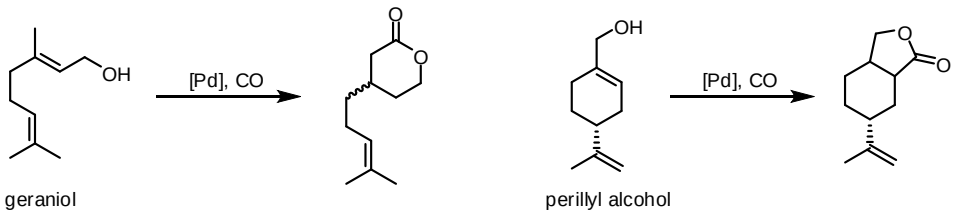
Following the results obtained in intermolecular carbonylation of alkenes in the presence of alcohols, it seemed credible that an alkene–bearing alcohol functionality would react in an intramolecular way giving a cyclic ester as the main product. Thus, the carbonylation of hydroxyalkenes was investigated for the selective preparation of lactones. In 1984 Semmelhack and co-workers reported the first attempts of intramolecular alkoxycarbonylation of alkenes. Reactions were catalyzed by $PdCl_2$ with $CuCl_2$, as a stoichiometric oxidant, in the presence of methanol under atmospheric pressure of CO. Under these conditions, no lactones were formed while tetrahydrofuran or tetrahydropyran rings bearing a methoxyester moiety were obtain from various hydroxyalkenes.[76] Butenol derivatives were converted selectivity into γ-butyrolactones conducing the reaction with the same condition described previously ($PdCl_2/CuCl_2$/MeOH).[76] The mechanism of this dicarbonylation proceed first of all with alcohol oxidative addition on a palladium and a lactonization step, followed by a methoxycarbonylation step (Scheme 35).[77]

[71] Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707.
[72] James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810.
[73] a) Inomata, K.; Toda, S.; Kinoshita, H. *Chem. Lett.* **1990**, 1567. b) Toda, S.; Miyamoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600.
[74] Cipres, I.; Jenk, J.; Kalck, Ph. *J. Mol. Catal. A* **1990**, *58*, 387.
[75] Chenal, T.; Cipres, I.; Jenk, J.; Kalck, Ph.; Perez, Y. *J Mol Catal A* **1993**, *78*, 351.
[76] Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496.
[77] Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1991**, *56*, 1099



Scheme 35. Proposal of a mechanism for the intramolecular alkoxycarbonylation of 3-butenol derivative.

Changing the palladium-based catalyst, tertiary and secondary allylic alcohol reacted to give lactones. The reaction required neutral condition and the absence of an oxidant, moreover the catalyst system is formed from $Pd(OAc)_2$ with a diphosphine ligands.[78] Another example is the intramolecular alkoxycarbonylation of monoterpenic alcohol, it is interesting because of the possibility to produce different lactones from natural hydroxylalkenes. As example, gerianiol, which have an allylic function and a trisubstituted double C=C bond is carbonilated to the corresponding six-membered lactone while the alkoxycarbonylation on a perillyl alcohol produced a five-member lactone (Scheme 36).[79] In the first case an isomerization step of internal double C=C bond of the allylic alcohol to terminal double C=C bond occur, meanwhile with the perillyl alcohol the isomerization does not take place.



Scheme 36. Cyclocarbonylation of geraniol and perillyl alcohol.

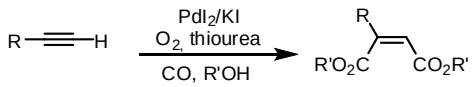
During the years, the attractive asymmetric version of alkoxycarbonylation of alkenes has been developed. Different chiral ligands were used with palladium-based catalyst by several

[78] El Ali, B.; Alper, H. *J. Org. Chem.* **1991**, 56, 1099.
[79] a) Nguyen, D. H.; Hébrard, F.; Duran, J.; Polo, A.; Urrutigoïty, M.; Kalck, Ph. *Appl. Organometal. Chem.*, **2005**, *19*, 30. b) El Ali, B.; Alper, H. *Synlett* **2000**, *2*, 161.

research groups.[80] Enantioselectivity up to 93% was achieved in the case of bis-methoxycarbonylation of styrene with palladium catalyst with antropisomeric diphosphine ligands.[81] Also the intramolecular alkoxycarbonylation reactions was achieved with a good result into products enantiselectivity, for example β-substituted allylic alcohols are carbonylated using $Pd(OAc)_2$ with a chiral diphosphine.[82]

The reaction of intermolecular alkoxycarbonylation of alkynes can produce various mono- and bis-alkoxy unsaturated products based on the catalytic system and reactions conditions. In 1994 Brandsma, starting from the first observation done by Tsuji, reported the alkoxycarbonylation of substituted acetylenes. Products of the reaction are acetylenic esters and the catalytic system involved was $PdCl_2$ with stoichiometric amounts of $CuCl_2$ in basic condition.[83] In this case the triple bond is maintained because of the C–H attivation by copper. Otherwise, propyne was converted into methyl methacrylate using a palladium(II) complex containing a 2-pyridylphosphine ligand in the presence of an acid whose conjugated base is a weakly coordinating ligand. The P-N ligand plays the role of chelating agent but also a proton messenger to the active palladium center when it acts as mono-cordinating P ligand.[84] Alkynes are converted into unsaturated ester with a different alcohols such as tert-butanol and iso-propanol with high regioselectivity but in moderate yields, using a catalytic system based on $Pd(OAc)_2$ and 1,4-bis(diphenylphosphino)butane.[85]

On the alkynes is also possible to add two CO building block in a presence of oxidant to obtain a diester. As example, a terminal alkyne in presence of PdI_2, stabilized by an excess of KI, and a robust ligand like thiourea is transformed into maleic esters (Scheme 37).[86]



Scheme 37. Bisalkoxycarbonylation of terminal alkynes.

As regards the intramolecular alkoxycarbonylation of alkynes, various palladium complexes catalyzed the lactonization of alkynols. For example, β- or γ- lactone derivatives with α-(alkoxycarbonyl)ethylene chain were synthesized from propynols and butynols, using a Pd-

[80] a) Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun*. 1990, 135. b) Sperrle, M.; Consiglio, G. *J. Mol. Catal. A: Chem.* **1999**, *143*, 263. c) Nozaki, K., Kantam, M. L.; Horiuchi, T.; Takaya, H. *J. Mol. Catal. A: Chem.* **1997**, *118*, 247.

[81] Nefkens, S. C.; Sperrle, M.; Consiglio, G. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1719.

[82] a) Alper, H.; Leonard, D. *J. Chem, Soc., Chem. Commun*. **1985**, 511.b) Alper, H.; Leonard, D. *Tetrahedron Lett.* **1985**, *26*, 5639.

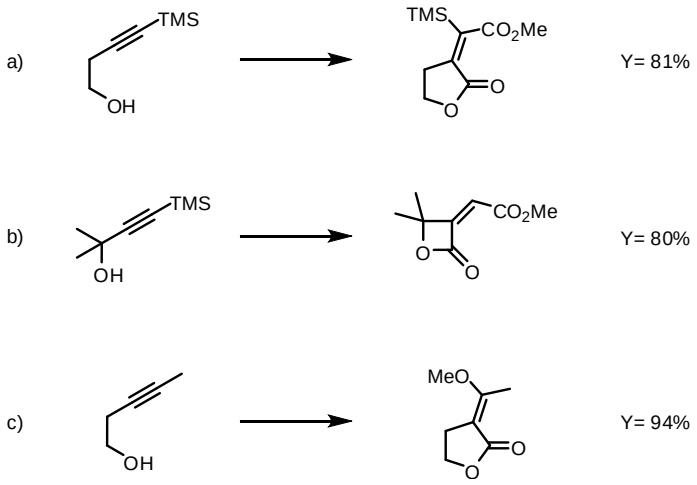
[83] a) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.***1980**, *21*, 849. b) Vasilesky, S. F.; Trofinov, B. A.; Mal'kina, A. G.; Brandsma, L. *Synthetic Comm.* **1994**, *24*, 85.

[84] a) Drent, E.; Arnoldy, P.; Budzelaar, P. H. M. *J. Organomet. Chem.* **1993**, *455*, 247. b) Drent, E.; Arnoldy, P.; Budzelaar, P. H. M. *J. Organomet. Chem.* **1994**, *475*, 57.

[85] El Ali, B.; Alper, H.; *J. Mol. Catal.* **1991**, *67*,29.

[86] a) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1995**, *503*, 21. b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219. c) Bonardi, A.; Costa, M.; Gabriele, B.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun.* **1994**, 2429.

catalyst/oxidant system (Scheme 38).[87] This reaction leads exclusively to *cis*-dicarbonylated product while if the TMS on butynol is replaced by alkyl of aryl substituent the trans-alkoxycarbonylation occurs on the alkynes (Scheme 38, c)



Scheme 38. Bis-carbonylation of various butynols or propynols.

Carbonylation of unsaturated substrate has been known for for decades but the reaction selectivity has been progressively improved. Palladium have a privileged role in this chemistry and its versatility allows the use of mild conditions for the selective incorporation of CO into acyclic and cyclic compounds.

[87] a) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1991**, *56*, 1099. b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun.* **1994**, 1429. c) Gabriele, B.; Salerno, G.; Di Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Chem. Soc. Perkin Trans.* **1997**, *1*, 147.

3.6 Aryl α-Diimine Ligand

In coordination chemistry, a ligand is an ion or molecule that is able to bind the central metal atom to form a coordination complex and it has a central role for the efficiency of the catalyst. Indeed the easily varied steric and electronic proprieties of α-diimine ligands are an important feature of transition metal α-diimine catalyst system (Figure 3)

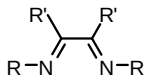


Figure 3. General chemical structure of α-diimine ligands.

The α-diimine ligands are well-known to stabilize organometallic complexes and they have important applications,[88] such as in olefin polymerization.[89] These ligands are easy to synthesize through the condensation of a diketone with two equivalent of an alkyl- or arylamine, often catalyzed by a Lewis or Brønsted acid. The backbone and aryl substituents are readily varied, allowing the preparation of arrays of ligands with independent control over the steric and electronic effects at the metal center. Brookhart and co-worker reported for the first time a family of a new cationic Pd(II) and Ni(II) α-diimine catalyst and it represent a real innovation in the development of classes of polymerization catalysts.[90] Catalysts developed by Brookhart, consisting of a late transition metal, such as nickel(II) or palladium(II), coupled with a bulky diimine ligand (Figure 4), that is able to polymerize ethylene, α-olefins and cyclic olefins and the copolymerization of nonpolar olefins and in general a variety of polyfunctionalized olefins.[91]

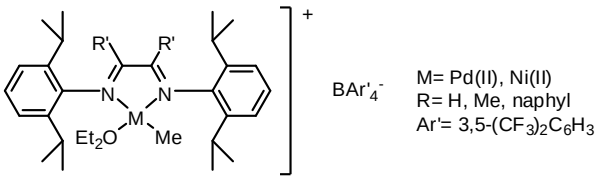
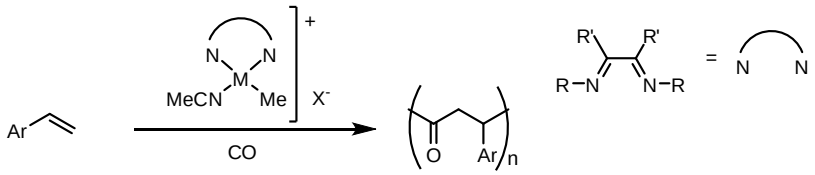


Figure 4. Brookhart's late metal diamine olefin polymerization catalyst.

The α-diimine catalysts have key characteristics for the polymerization of olefins such as highly electrophilic cationic metal center, that improve the rates of olefin insertion. The use of non-coordinating counterions provides an accessible coordination site for incoming olefins. In

[88] a) tom Dieck, H.; Svoboda, M.; Grieser, T. *Z. Naturforsh* **1981**, *36b*,832.
[89] a) Huang, Y.-B.; Tang, G.-R.; Jin, G.-Y.; Jin, G.-X. *Organometallics* **2008**, *27*, 259. b) McKnight, A. L.; Waymouth, R. M. *Chem. Rev.* **1998**, *98*, 2587 c) Appukuttan, V. K.; Liu, Y.; Son, B. C.; Ha, C.-S.; Suh, H.; Kim, I. *Organometallics* **2011**, *30*, 2285. d) Cho, W.; Cho, H.; Lee, C. S.; Lee, B. Y.; Moon, B.; Kang, J. *Organometallics* **2014**, *33*, 1617–1622.
[90] Johnson, L. K.; Killian, C. M.; Brookhart, M. *J. Am. Chem. Soc.* **1995**, *117*, 6414.
[91] a) Killian, C. M.; Tempel, D. J.; Johnson, L. K.; Brookhart, M. *J. Am. Chem. Soc.* **1996**, *118*, 11664. b) Brookhart, M. S.; Johnson, L. K.; Killian, C. M.; Arthur, S. D.;Feldman, J.; McCord, E. F.; McLain, S. J.; Kreutzer, K. A.; Bennett, A. M. A.; Coughlin, E. B.; Ittel, S. D.; Parthasarathy, A.; Tempel, D. J. WO Patent Application 9623010 to DuPont, April 3, 1995. c) Abu-Surrah, A. S.; Rieger, B. *Angew. Chem., Int. Ed. Engl.* 1996, *35* (21), 2475.

the field of copolymerization the research group, in which I spent my PhD studies, have deep investigated the copolymerization between carbon monoxide and styrene or *p*-methylstyrene promoted by Palladium(II)–diimine catalysts (Scheme 39). They focused the attention particularly on the regio- and sterocontrol on the CO/styrene copolymerization printed by ligands and conteurions and by the characterization of key intermediates of the copolymerization.[92]



Scheme 39. Generic examples for copolymerization of CO/vinylarenes.

The α-diimine is a very useful ligand and the studies around its role in the organometallic chemistry is not close but in continuous extension. For example very recently α-diimine ligands are reported as non-innocent ligand that has been reduced to its radical monoanionic form (L•⁻), which (together with the doubly reduced dianion) can effectively stabilize low-valent metal, such as cobalt (I) complexes, leading to a rich variety of novel structures.[93]

[92] a) Binotti, B.; Bellachioma, G.; Cardaci, G.; Carfagna, C.; Zuccaccia, C.; Macchioni, A. *Chem. Eur. J.* **2007**, *13*, 1570−1582. b) Carfagna, C.; Gatti, G.; Martini, D.; Pettinari, C. *Organometallics* **2001**, *20*, 2175. c) Carfagna, C.; Gatti, G.; Paoli, P.;. Binotti, B.; Fini, F.; Passeri, A.; Rossi, P.; Gabriele, B. *Organometallics* **2014**, *33*, 129.

[93] a) Yang, X.-J.; Fan, X.; Zhao, Y.; Wang, X.; Liu, B.; Su, J.-H.; Dong, Q.; Xu, M.; Wu, B. *Organometallics* **2013**, *32*, 6945. b) Wang, X.; Zhao, Y.; Gong, S.; Liu, B.; Li, Q.-S.; Su, J.-H.; Wu, B.; Yang, X.-J. *Chem. Eur. J.* **2015**, *21*, 13302.

4. Scope of the Thesis

The aryl α-diimine compounds are well-known ligands used in organometallic chemistry. They might be employed together with transition metals to attain a variety of complexes able to catalyze a wide range of reactions.

In this PhD thesis I investigated the catalytic behavior of Pd(II) complexes containing aryl α-diimine ligands (DAB) for the oxidative carbonylation of unsaturated substrates. Although DAB ligands are stable, accessible, and efficient as ligands to palladium, they have not been used so far in the oxidative carbonylation. Due to the know-how of the group, in which I worked as a PhD student, in the CO/styrene copolymerization reaction promoted by aryl α-diimine-Pd(II) complexes, I began a deep investigation on the use of these proficient ligands in the palladium-catalyzed oxidative carbonylation.

Considering the ability of the oxidative carbonylation to convert low cost substrates into high valuable products, the aim of this thesis is to develop an efficient Palladium(II)-catalyzed methodology able to synthesize quite important building blocks with high yield, selectivity and a wide range of application by using mild reaction conditions.

5. Bis-alkoxycarbonylation of Olefins

5.1 Introduction

Oxidative carbonilations are among the most important reactions in the field of palladium homogeneous catalysis [45,94] and since they allow one to directly convert low value materials, like olefins and carbon monoxide, into a number of highly valuable carbonylated compounds, useful in synthetic organic chemistry as well as and in pharmaceutical and medicinal chemistry. The reaction was discovered by Tsuji and co-workers in 1964 reporting the reaction of olefin-palladium chloride complexes with CO to produce β-chloroacyl chlorides.[48a,95] Cloroesters are obtained from both internal and terminal aliphatic olefins when the reaction was conducted in alcohols. Another version of the bis-alkoxycarbonylation of olefins was reported by Heck, using mercuric chloride as additive.[96] Succinic acid and its derivatives (Figure 5, A) are important compounds, as they find application in material science[97] (Figure 5, D) and the synthesis of inhibitors of renin[98] (Figure 5, C) and matrix metalloproteinase (Figure 5, B).[99]

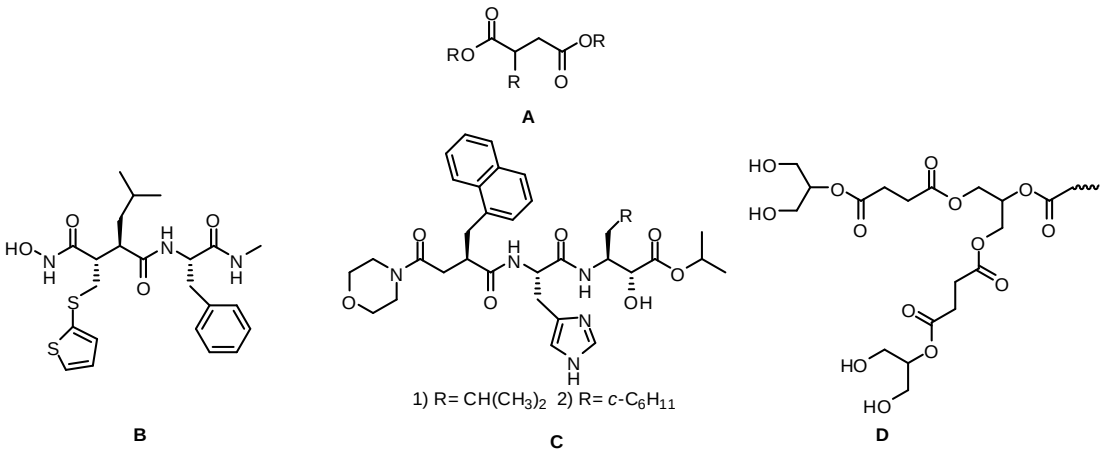
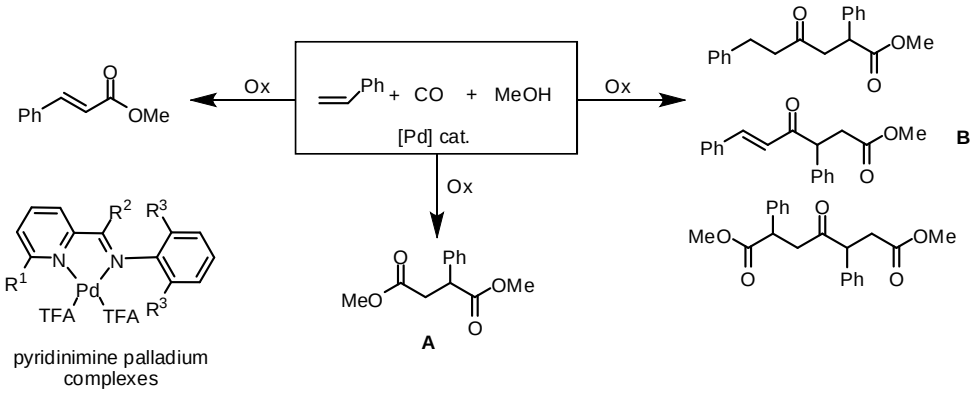


Figure 5. Chemical structure of inhibitors of matrix metalloproteinase (B), inhibitors of renin (C) and fragment of dendrimer (D) based on glycerol.

[94] a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. b) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825; c) Liu, Q.; Zhang, H.; Lei, *Angew. Chem. Int. Ed.* **2011**, *50*, 10788.
[95] Tsuji, J.; Morikawa, M.; Kiji, J. *J. Am. Chem. Soc.* **1964**, *86*, 4851.
[96] Heck, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 2712.
[97] a) Livage, C.; Egger, C.; Ferey, G. *Chem. Mater.* **2001**, *13*, 410. b) Carnahan, M. A.; Grinstaff, M.W.; *Macromolecules* **2001**, *34*, 7648. c) Qiu, Z.; Ikehara, T.; Nishi, T. *Macromolecules* **2002**, *35*, 8251. d) Okajima, S.; Kondo, R.; Toshima, K.; Matsumura, S. *Biomacromolecules* **2003**, *4*, 1514. e) Dong, T.; Shin, K.; Zhu, B.; Inoue, Y. *Macromolecules* **2006**, *39*, 2427. f) Carnahan, M. A.; Grinstaff, M. W. *Macromolecules* **2006**, *39*, 609.
[98] a) Yoshikawa, K.; Inoguchi, K.; Morimoto, T.; Achiwa, K. *Heterocycles* **1990**, *31*, 1413. b) Ito, Y.; Kamijo, T.; Harada, H.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 2731 c) Inoguchi, K.; Morimoto, T.; Achiwa, K. *J. Organomet. Chem.* **1989**, *370*, C9; d) Jendralla, H. *Tetrahedron Lett.* **1991**, *32*, 3671; e) Kammermeier , B.; Beck, G.; Holla, W.; Jacobi, D.; Napierski, B.; Jendralla, H. *Chem. Eur. J.* **1996**, *2*, 307.
[99] a) Whittaker, M.; Floyd, C. D.; Brown, P.; Geraing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735; b) Sibi, M. P.; Hasegawa, H. *Org. Lett.* **2002**, *4*, 3347.

The direct synthesis of succinic acid ester is also possible by using Pd-catalyzed oxidative bis-alkoxycarbonylation of olefins from simple and readily available feedstocks. After the pioneering work by Heck,[96] a big rush was made by Chauvin and co-workers in 1990.[100] They reported the synthesis of dibutyl succinates with moderate selectivities under mild reaction conditions: pressure of carbon monoxide of 45 bar and a temperature between 60-80°C, but with a catalytic efficiency up to 300 TON, by employing butyl nitrile as the oxidizing agent.[100] In 2001, Bianchini and co-workers described a detailed study on the bis-alkoxycarbonylation of styrene, using pyridinimine ligands. $Pd(TFA)_2$ as the palladium source and benzoquinone as oxidant.[101] The overall conversion of styrene to carbonylated products and the reaction selectivity have been studied by systematically varying the type of palladium initiator, the concentrations of organic oxidant and protic acid and CO pressure.

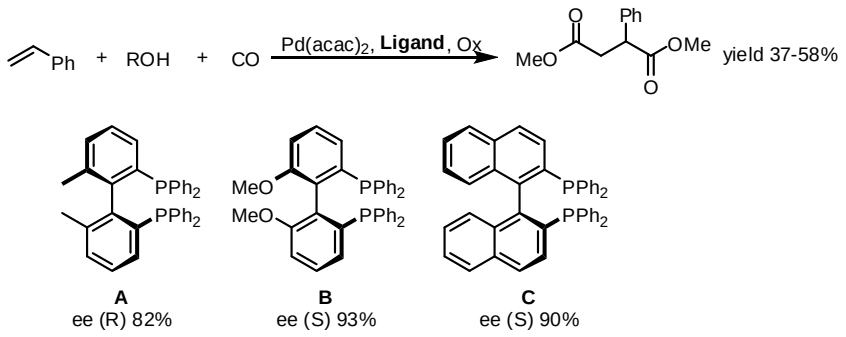


Scheme 40. Oxidative carbonylation catalyzed by pyridinimine palladium complexes.

Indeed the selectivity of 98% in dimethylphenylsuccinate (Scheme 40, A) was obtain by an appropriate choice of the pyridinimine ligand. The addition of two equivalents of TsOH to the catalytic mixture increased the styrene conversion but lowered the selectivity in the dimethyl phenylsuccinate due to greater production of methyl 3,6-diphenyl-4-oxohexanoate (Scheme 40, B).[101]

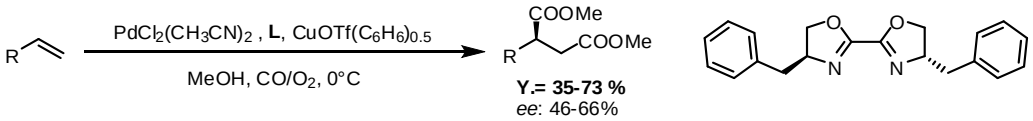
Together with the racemic approach, asymmetric versions of bis-alkoxycarbonylation of olefins have studied during recent years. In the literature two different main approaches have been reported using several chiral diphoshine palladium complexes, obtaining dimethyl phenylsuccinate with high enantioselection. Consiglio and co-workers reported the enantioselective version of the bis-alkoxycarbonylation of alkene by using chiral ligands as DIOP [(–)2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] and BINAP [2,2'-bis(diohenylphosphino)-1,1'-bisnaphthyl] (Scheme 41, A) and benzoquinone as a oxidant (Scheme 41).[80b,81]

[100] Bréchot, P.; Chauvin, Y.; Commereuc, D.; Saussine, L. *Organometallics* **1990**, *9*, 26.
[101] Bianchini, C.; Man Lee, H.; Mantovani, G.; Meli, A.; Oberhauser, W. *New J. Chem.* **2002**, *26*, 387.



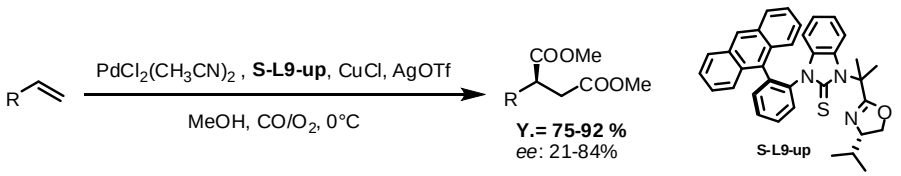
Scheme 41. Palladium-catalyzed enantioselective bis-alkoxycarbonylation of olefins.

More recently, Chan an co-workers made the use of modified dipyridylphosphine cationic Pd(II) complexes to obtain good chemoselectivity and enatiomeric excess.[102] Although the high enantioselection, in both cases dimethyl phenylsuccinate was obtained in modest conversion and selectivity, under an elevated carbon monoxide pressure. On the other hand, Inomata and Huang used chiral N,N and N,S ligands in combination with Pd(II)/Cu(II) salts and oxygen. The Inomata's asymmetric version for the synthesis of diesters was developed by using a chiral bisoxazoline ligand in presence of Cu(I) triflate at 25°C to obtain enantiomerically enriched diesters in good yields with up to 66% *ee* (Scheme 42).[103]



Scheme 42. Palladium-catalyzed oxidative carbonylation of olefins.

Meanwhile, Huang and co-workers reported the oxidative carbonylation of terminal olefins to phenylsuccinate esters by using chiral thiourea-oxazolines as the ligand (Scheme 43).[104]



Scheme 43. Enantioselective bis-alcoxycarbonylation using thioureas as ligand.

In both cases the bis-alkoxycarbonylation of different styrenes were achieved with a high catalyst loading, under reaction conditions, moderate enantioinductions and yields.
Although these contributions are important, a good methodology to synthesize succinic acid esters with complete conversion and selectivity, under mild reaction conditions, is still lacking. In addition, reactions carried out in the presence of oxygen bring up security issues

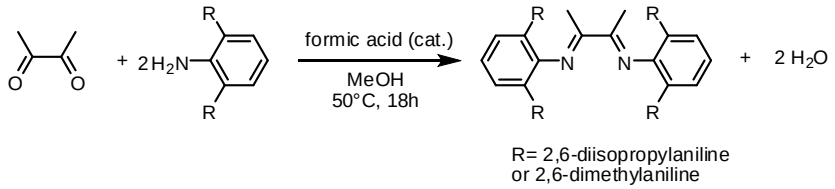
[102] Wang, L.; Kwok, W.; Wu, J.; Guo, R.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, A. S. C.; Chan, K.-S. *J. Mol. Catal. A* **2003**, *196*, 171.
[103] Takeuchi, S.; Ukaji, Y.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 955.
[104] Gao, Y.-X.; Chang, L.; Shi, H.; Liang, B.; Wongkhan, K.; Chaiyaveij, D.; Batsanov, A. S.; Marder, T. B.; Li, C.-C.; Yang, Z.; Huang, Y. *Adv. Synth. Catal.* **2010**, *352*, 1955.

especially for a bench-scale process.[105] Our group has extensively studied the catalytic behaviour of aryl α-diimine (N,N-diaryl-diazabutadiene, DAB) Pd(II) complexes in the CO/styrene copolymerization with good results in terms of copolymer tacticity and yields. [106] Despite the stability, the prowess as palladium ligand and the easy accessibility,[107] DAB ligands were never applied to the bis-alkoxycarbonylation reaction, moreover we figured out a quite close structural relationship with bisoxazoline ligands, used by Inomata and co-workers, [103,108] for this type of reactions. Therefore, we undertook an extensive study on the use of these proficient ligands in the palladium-catalyzed oxidative carbonylation of olefins to succinic acid diesters.

5.2 Result and Discussion

5.2.1 Synthesis of Aryl a-Diimine Ligands

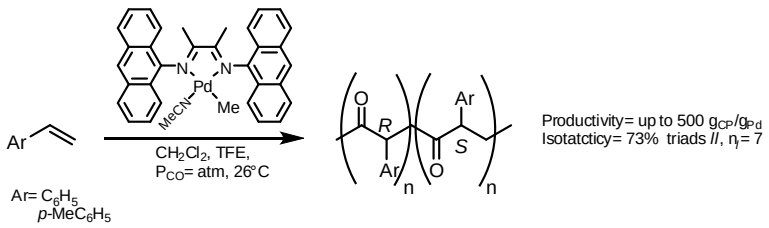
The α-diimine ligands are well-known to stabilize organometallic complexes [88,109] The synthesis is a simple condensation reaction between an α-diketone and two equivalents of an alkyl- or arylamine, often catalyzed by a Lewis or Brönsted acid. As an example, the synthesis of (2,6-MePh)$_2$DABMe$_2$ and (2,6-*i*-PrPh)$_2$DABMe$_2$ (DAB= 1,4-diazabutadiene) start from 2,3-butandione which reacts respectively with 2,6-dimethylaniline and 2,6-diisopropylaniline in the presence of a catalytic amount of formic acid (Scheme 44).



Scheme 44. Synthesis of aryl α-diimine ligands.

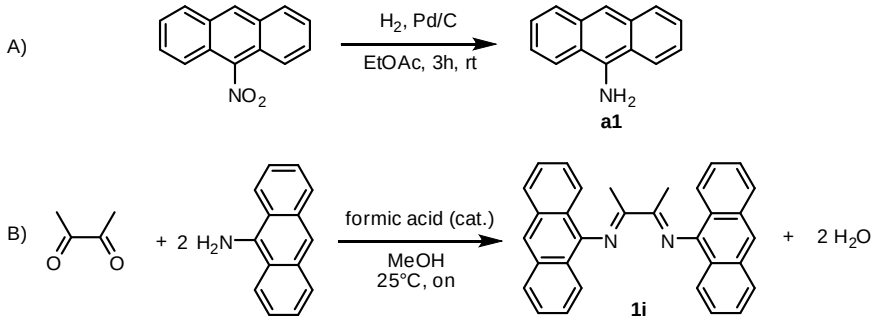
Recently, the research group, in which I spent my PhD studies, has reported for the first time a new aryl α-diimine ligand with extended aromating rings, bis-(9-antracenil)-2,3-dimetil-1,4-diazabutadiene [(9-C$_{14}$H$_9$)$_2$DABMe$_2$]. The ligand was employed in the palladium-catalyzed copolymerization reaction, between carbon monoxide and styrene (Scheme 45).[106a] The products are a stereoblock isotactic copolymer CO/*p*-methylstyrene and CO/styrene polyketones in yields that are the highest reported for the stereoselective copolymerization of aromatic olefins with carbon monoxide, using achiral nitrogen ligands. [106a]

[105] Zlochower, I. A.; Green, G. M. *Journal of Loss Prevention in the Process Industries* **2009**, *22*, 499.
[106] a) Carfagna, C.; Gatti, G.; Paoli, P.; Binotti, B.; Fini, F.; Passeri, A.; Rossi, P.; Gabriele, B. *Organometallics* **2014**, *33*, 129. b) Carfagna, C.; Gatti, G.; Paoli, P.; Rossi, P. *Organometallics* **2009**, *28*, 3212; c) Carfagna, C.; Gatti, G.; Mosca, L.; Passeri, A.; Paoli, P.; Guerri, A. *Chem. Commun.* **2007**, *43*, 4540.
[107] Ittel, S. D.; Johnson, L.; Brookhart, M. *Chem. Rev.* **2000**, *100*, 1169.
[108] Carfagna, C.; Gatti, G.; Mosca, L.; Natanti, P.; Paoli, P.; Rossi, P.; Gabriele, B.; Salerno, G. *Dalton Trans.* **2011**, *40*, 6792.
[109] a) Van Asselt, R.; Elsevier: C. J.; Smeets, W. J. J.; Spek, A. L.;Benedix, R. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 88. b) Van Koten, G.; Vrieze, K. *Adv. Organomet. Chem.* **1982**, *21*, 151.



Scheme 45. Copolymerization of CO/vinylarene promoted by a new palladium catalyst.

The ligand [(9-$C_{14}H_9$)$_2$DABMe$_2$] **1i** is synthesized starting from 9-nitroanthracene that is reduced thanks to palladium on charcoal (10% $^{w}/_{w}$) giving 9-aminoanthracene **a1** (9-$C_{14}H_9$)NH_2 (Scheme 46, A). Hereafter, the amine with extended aromating rings condenses with 2,3-butandione to give the desiderated ligand that precipitates in reaction mixture (Scheme 46, B).



Scheme 46. Hydrogenation reaction of 9-nitroanthracene and condensation reaction with α-diketone.

In our extensive study, around the palladium-catalyzed oxidative carbonylation of olefins to succinic acid diesters, we tested these proficient ligands starting from the more simple **1a** one to the new aryl α-diimine ligand **1i** with extended aromating rings. Aryl α-diimine ligands used for our initial experiments are reported in Figure 6.

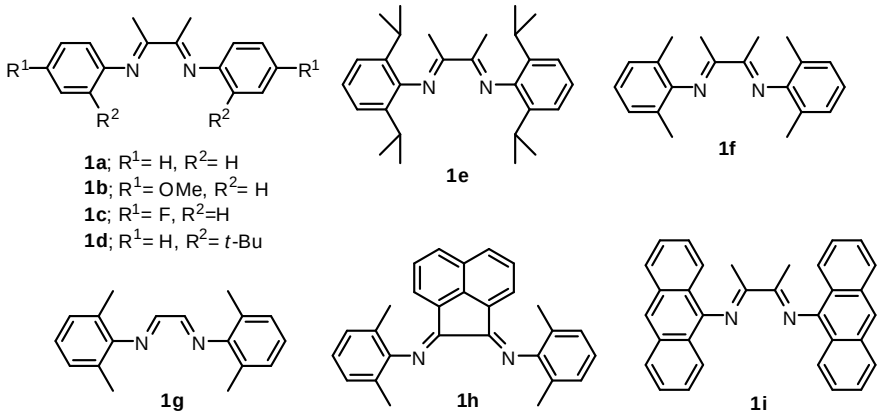
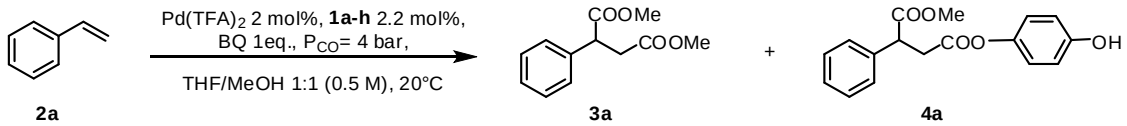


Figure 6. Aryl α-dimmine ligand 1a-i.

5.2.2 Oxidative Carbonylation on Olefins: Screening of α-diimine Ligands and Reaction Conditions

Our initial experiments for the oxidative bis-alkoxycarbonylation of olefins started from the use of styrene **2a**, as a olefin substrate, DAB ligands **1a-h** (Figure 6) and $Pd(TFA)_2$ as palladium source, in a 1:1 mixture of methanol/THF as reaction medium and BQ as useful and safe oxidizing agent to close the catalytic cycle.[110] Reactions were conducted under particularly mild conditions, under 4 bar of CO at 20 °C (Table 2).

Table 2. Bis-methoxycarbonylation reaction of styrene catalyzed by $Pd(TFA)_2$ with ligands 1a-h. Effect of the ligand and benzoquinone.



2a **3a** **4a**

Entry[a)]	Ligand **1a-h**	Time (h)	Conv. (%)[b)]	**3a**:**4a** ratio[b)]
1	--	42	<5	ND
2	**1a**	42	50	50:0
3	**1b**	170	40	40:0
4	**1c**	170	25	25:0
5	**1d**	72	40	40:0
6	**1e**	42	70	60:10
7	**1f**	72	90	75:15
8	**1g**	48	40	40:0
9	**1h**	72	85	65:20
10[c)]	**1f**	21	≥98	87:13
11[d)]	**1f**	42	≥98	65:35
12[e)]	**1f**	42	30	28:2

a) Reaction performed in autoclave at P_{CO}=4 bar, with styrene (2 mmol scale), 2 mol% of $Pd(TFA)_2$, 2.2 mol% of **1a–h** and 1 equiv. of BQ with THF/MeOH 1:1 (0.5 M) as reaction medium.

b) Determined by direct ^{1}H NMR analysis of a sample of the reaction mixture.

c) Reaction performed with 1.5 equiv. of BQ.

d) Reaction performed with 0.5 mol% of $Pd(TFA)_2$, 0.55 mol% of **1f** and 1.5 equiv. of BQ.

e) Reaction performed with 0.1 mol% of $Pd(TFA)_2$, 0.11 mol% of **1f** and 1.5 equiv. of BQ.

No product was formed without ligand, (Table 2, entry 1), whereas the use of ligands **1a–c**, bearing unsubstituted or *para*-substituted aryl groups, (Figure 6) the reaction afforded the formation of dimethyl succinate **3a**, with modest but encouraging conversions (Table 2, entries 2–4). The mono-*ortho*-*tert*-butyl substituted ligand **1d** (Table 2, entry 5) gave the similar result. On the other hand, using the *ortho*-disubstituted-diaryl DAB ligands **1e–f** bearing bulky isopropyl groups (**1e**) or methyl groups (**1f**) in the ortho positions of the aromatic rings, good conversions of styrene were attained into the desired product **3a** (Table 2, entries 6 and 7). The dimethoxy succinic acid **3a** was not the only product but the

[110] Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790.

formation of 4-(4-hydroxyphenyl) 1-methyl 2-phenylsuccinate **4a** occurred as by-product in different proportions, due to the participation of hydroquinone as nucleophile in the carbonylation reaction. The hydroquinone is the product of the reduction of benzoquinone under the reaction conditions.

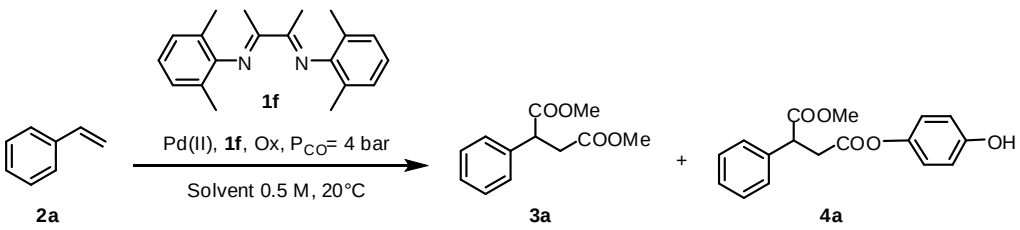
No beneficial effects were reached using the ligand **1h**, bearing diverse diimine backbone, compared to ligands **1f** e **1g** (Table 2, compare entry 9 with entries 7 and 8). On the other hand, when the amount of benzoquinone was increase up to 1.5 equiv, a complete conversion of styrene into the products was achieved. In this condition, with the *ortho*-dimethyl disubstituted ligand **1f** (Table 2, entry 10) the ratio between **3a:4a** was 87:13.

In this context the real efficiency of $Pd(TFA)_2$/**1f** catalyst was surveyed by performing the bis-alkoxycarbonylation reaction with much lower catalyst loading (0.5 mol%). Complete conversion was reached although with an increased amount of **4a** and a prolonged reaction time (Table 2, entry 11), even at 0.1 mol% the catalyst $Pd(TFA)_2$/**1f** was still active converting 30% of styrene **2a** in 42 h (Table 2, entry 12).

With this data in hand an extensive optimization of the reaction was carried out, especially trying to decrease the amount of by-product **4a** (Table 2).

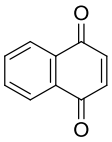
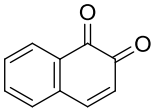
In the Table 3 results of bis-methoxycarbonylation reaction of styrene, catalyzed by $Pd(TFA)_2$, in the presence of ligand **1f,** changing the organic oxidant and solvent system are reported.

Table 3. Bis-methoxycarbonylation reaction of styrene catalyzed by $Pd(TFA)_2$ with ligand 1f. Effect of the oxidant and solvent.



2a **3a** **4a**

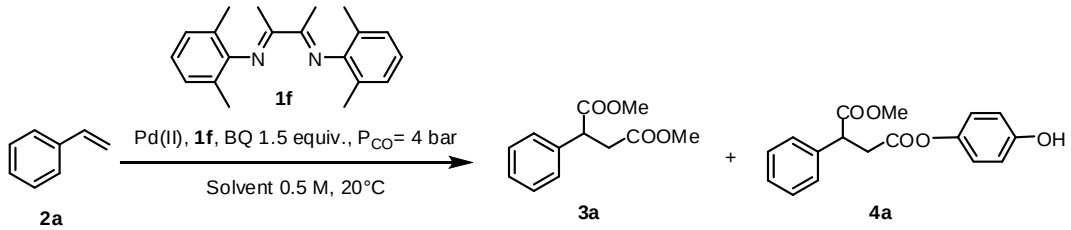
Entry[a)]	Metal	Ox	Solv.	Conv.[b)]	Note[b)]
1	$Pd(TFA)_2$ 0.5 mol%	BQ 1.5 eq.	THF/MeOH 7:1	≤5 %	--
2	$Pd(TFA)_2$ 0.5 mol%	BQ 1.5 eq.	THF/MeOH/CH_2Cl_2 1:1:6	50 %	40 % **3a** 10 % **4a**
3	$Pd(TFA)_2$ 0.5 mol%	BQ 1.5 eq.	THF/MeOH/Toluene 1:1:6	20 %	--
4	$Pd(TFA)_2$ 0.5 mol%	DDQ 1.5 eq.	THF/MeOH 1:1	≤5 %	--
5	$Pd(TFA)_2$ 0.5 mol%	BQ 1.5 eq.	THF/MeOH 7:1	≥98%	75 % **3a** 25 % **4a**

6	$Pd(TFA)_2$ 0.5 mol%	 1.5 eq.	THF/MeOH 1:1	≤5 %	--
7	$Pd(TFA)_2$ 0.5 mol%	 1.5 eq.	THF/MeOH 1:1	≤5 %	--

a) Reaction performed in autoclave for 42h at P_{CO} = 4 bar, with styrene (2 mmol-scale), Pd(II) 0.5 mol% (0.01 mmol), Ligand **1f** 0.55 mol% (0.011 mmol,) and the oxidant in the stated reaction medium.
b) Determined by using ^{1}H NMR analysis of a direct sample of the reaction mixture.

No reaction took place using DDQ as organic oxidants (much stronger oxidizing agent than benzoquinone). From this screening, a beneficial effect thanks to the increasing of the MeOH/THF ratio on selectivity was emerged. In fact using **1f** as ligand with the 7:1 MeOH/THF mixture as reaction medium, the ratio **3a**:**4a** ratio was 75:25 (Table 3, entry 5; to be compared with entry 11 of Table 2) and was more favourable for the product **3a**

Table 4. Bis-methoxycarbonylation reaction of styrene catalyzed by Pd (II) with ligand 1f. Effect of the additive.



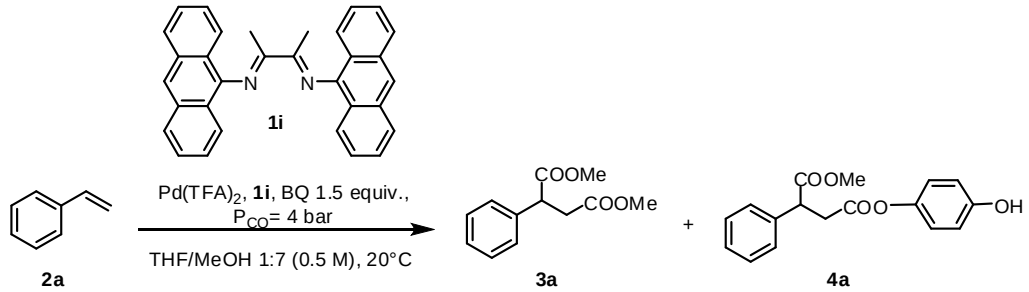
Entry[a)]	Metal	Additive	Solv.	Conv.[b)]	Note[b)]
1	$Pd(TFA)_2$ 0.5 mol%	-	THF/MeOH 7:1	≥98%	75 % **3a**, 25 % **4a**
2	$Pd(TFA)_2$ 0.5 mol%	*p*-TSA 2 mol%	THF/MeOH 7:1	90%	80 % **3a**, 20 % **4a**
3	$Pd(TFA)_2$ 0.1 mol%	-	THF/MeOH 7:1	25%	25 % **3a**, 0 % **4a**
4	$Pd(TFA)_2$ 0.1 mol%	*p*-TSA 0.5 mol%	THF/MeOH 7:1	75%	65% **3a**, 10 % **4a**

a) Reaction performed in autoclave for 42h at P_{CO} = 4 bar, with styrene (2 mmol-scale), Pd(II) 0.5 mol% or 0.1 mol% (0.01 or 0.002 mmol), Ligand **1f** 0.55 mol% or 0.11 mol% (0.011 mmol, 0.0022 mmol) and the oxidant in the started reaction medium.
b) Determined by using ^{1}H NMR analysis of a direct sample of the reaction mixture.

Moreover the presence of *p*-TSA appeared to be of a great importance, with a quantity of sulfonic acid four to five times the amount of palladium, an exceptional increment of efficiency of the process was achieved, comparing entry 4 in Table 4 with entry 12 in Table 2, the improvement was evident with **3a**:**4a** ratio of 65:10 (Table 4, entry 4). In this case, with lower catalyst loading down to 0.1 mol%, the catalytic TON and TOF were respectively of 750 and 18 h^{-1}.

Continuing the process of optimization, we also tested the new ligand bis(9-anthryl)-2,3-dimethyl-1,4-diazabutadiene **1i**.[106a] By using of this ligand, the quantitatively convertion of the styrene has been possible with formation of less than 5% of by-product **4a** (Table 5, entry 1), thus resulting the best ligand for the oxidative carbonylation. Remarkably the catalyst $Pd(TFA)_2$/**1i** exhibits a certain degree of activity even at atmospheric pressure of CO (Table 5, entries 3 and 4)

Table 5. Bis-methoxycarbonylation reaction of styrene catalyzed by $Pd(TFA)_2$ with ligand 1i.



Entry[a)]	**Ligand**/amount of $Pd(TFA)_2$	Additive	Conv.[b)]	**3a**:**4a**[b)]
1	**1f**/0.5 mol%	*p*-TSA 2 mol%	≥98%	95:5
2	**1f**/0.1 mol%	*p*-TSA 0.5 mol%	45 %	45:0
3[c)]	**1f**/0.5 mol%	*p*-TSA 2 mol%	85 %	80:5
4[c)]	**1f**/0.1 mol%	*p*-TSA 0.5 mol%	25 %	25:0

a) Reaction performed in autoclave at P_{CO} of 4 bar, with styrene **2a** (2 mmol-scale), 0.5 or 0.1 mol% of $Pd(TFA)_2$, 0.55 or 0.11 mol% of **1f** or **1i**, and 1.5 eq. of BQ, with MeOH/THF 7:1 (0.5M) as the reaction medium. Time reaction 66h.

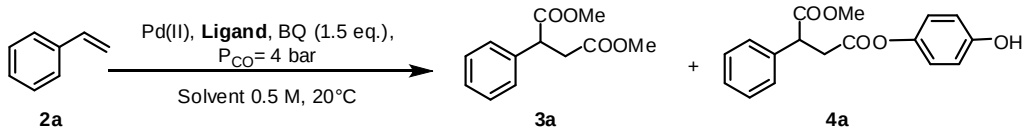
b) Determined by using ^{1}H NMR analysis on a direct sample of the reaction mixture.

c) Reaction performed in a Schlenk tube at atmospheric pressure of CO.

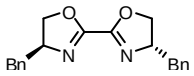
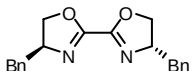
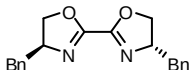
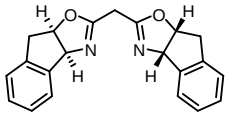
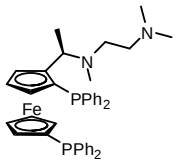
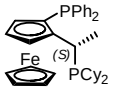
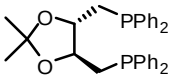
To highlight the importance of aryl α-dimine ligands in the olefin carbonylation reaction we screened various literature known ligands for Pd(II) complexes, such as bis-oxazoline[103] and

diphosphine ligands, [81,80b] in combination with $Pd(TFA)_2$, but no one resulted to be active in the bis-alkoxycarbonylation of the styrene (Table 6).

Table 6. Screening of various literature known ligand-Pd(II) complexes for the bis-methoxycarbonylation of styrene.



2a **3a** **4a**

Entry[a)]	Metal	**Ligand**	Additive	Solv.	Conv.[b)]
1	$Pd(TFA)_2$ 1 mol%	 1.1 mol%	--	THF/MeOH 1:1	≤5 %
2	$Pd(TFA)_2$ 1 mol%	 1.1 mol%	p-TSA 2 mol%	THF/MeOH 1:1	≤5 %
3	$Pd(TFA)_2$ 2 mol%	 2.2 mol%	p-TSA 2 mol%	THF/MeOH 1:1	≤5 %
4	$Pd(TFA)_2$ 2 mol%	 2.2 mol%	--	THF/MeOH 1:1	≤5 %
5	$Pd(TFA)_2$ 2 mol%	 2.2 mol%	--	THF/MeOH 1:1	≤5 %
6	$Pd(TFA)_2$ 0.5 mol%	 (*S*)-(R_p)-JOSIPHOS 0.55 mol%	p-TSA 2 mol%	THF/MeOH 1:7	≤5 %
7	$Pd(TFA)_2$ 0.5 mol%	 0.55 mol%	p-TSA 2 mol%	THF/MeOH 1:7	≤5 %
8	$Pd(TFA)_2$ 0.5 mol%	 (+)-DIOP 0.55 mol%	p-TSA 2 mol%	THF/MeOH 1:7	≤5 %

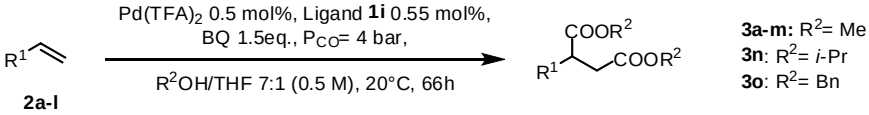
a) Reaction performed in autoclave at P_{CO} = 4 bar, with styrene (2 mmol-scale), Pd(II) 0.5 mol%, 1 mol% or 2 mol% (0.01, 0.02 or 0.04 mmol), ligands 0.55 mol%, 1.1 mol% or 2.2

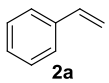
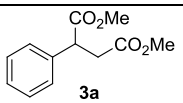
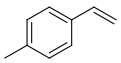
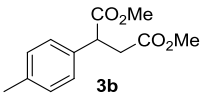
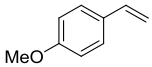
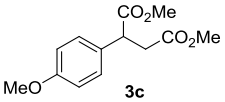
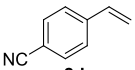
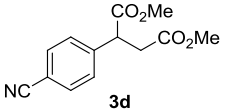
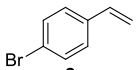
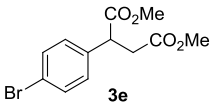
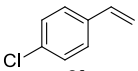
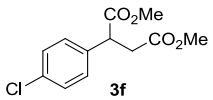
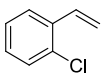
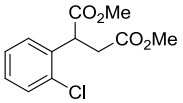
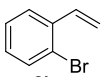
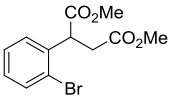
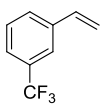
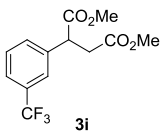
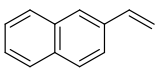
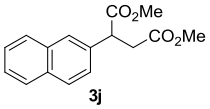
mol% (0.011 mmol, 0.022 or 0.044 mmol) and the oxidant (BQ 1.5 eq., 3 mmol) in the started reaction medium. Time reaction= 42h.
b) Determined by using ^{1}HNMR analysis of a direct sample of the reaction mixture.

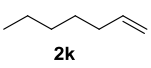
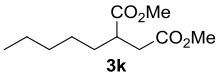
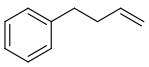
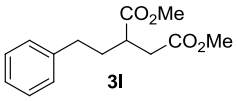
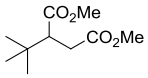
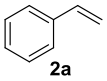
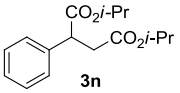
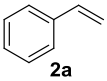
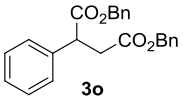
5.2.3 Oxidative Carbonylation on Olefins: Scope of the Reaction

The new efficient and selective catalytic system $Pd(TFA)_2$/**1i** was then applied to the bis-alkoxycabonylation of different vinylarenes and aliphatic to prove the generality of this new methodology (Table 7).

Table 7. Scope of the bis-alkoxycarbonylation reaction of aryl and alkyl olefins.



Entry[a]	2a-l	3a-n	Yield (%)[b]
1	 **2a**	 **3a**	91
2	 **2b**	 **3b**	97
3[c]	 **2c**	 **3c**	88[d]
4	 **2d**	 **3d**	90[d]
5	 **2e**	 **3e**	96
6	 **2f**	 **3f**	91
7	 **2g**	 **3g**	75[e] (94)
8	 **2h**	 **3h**	45[e] (91)
9	 **2i**	 **3i**	85
10[f]	 **2j**	 **3j**	87[d]

11[f)]	 **2k**	 **3k**	92
12[f)]	 **2l**	 **3l**	77
13[g)]	 **2m**	 **3m**	53[e)] (95)
14[h)]	 **2a**	 **3n**	92
15[h)]	 **2a**	 **3o**	94

a) Reactions performed in autoclave at a P_{CO} of 4 bar, with olefins **2a-l** (2 mmol-scale), 0.5 mol% of $Pd(TFA)_2$, 0.55 mol% of **1i**, 2 mol% of *p*-TSA and 1.5 eq. of BQ, in 7:1 MeOH/THF (0.5M) as the reaction medium, for 66 h.

b) Isolated yields after column chromatography.

c) Reaction performed with 1 mol% catalyst loading and 2 mol% of *p*-TSA in 7:1 MeOH/THF (0.25M) as the reaction medium

d) The presence of a small amount of by-products **4** (less than 7%) in the crude mixture was detected by ^{1}H NMR.

e) Conversion of the α-olefins and, in parenthesis, isolated yields of the converted product are reported.

f) Reaction performed with 1 mol% catalyst loading.

g) Reaction performed with 2 mol% catalyst loading.

h) Reaction performed with 2 mol% catalyst loading, using *i*-PrOH or BnOH in place of methanol.

The succinic acid methyl esters **3a–l** were achieved in good to excellent yields, despite the different electronic character of the substituents in the vinyl arene aromatic rings (Table 7, entries 1–10). The best isolated yield was reached using *para*-methylstyrene as substrate (Table 7, entry 2). In particular by using an olefin with a strong electrodonating groups such as *p*-OMe, a diluted reaction and a slight increase of catalyst loading were needed to balance the amount of the corresponding by-products **4** generated in the reaction, obtaining **3c** with 88 % yield (Table 7, entry 3).

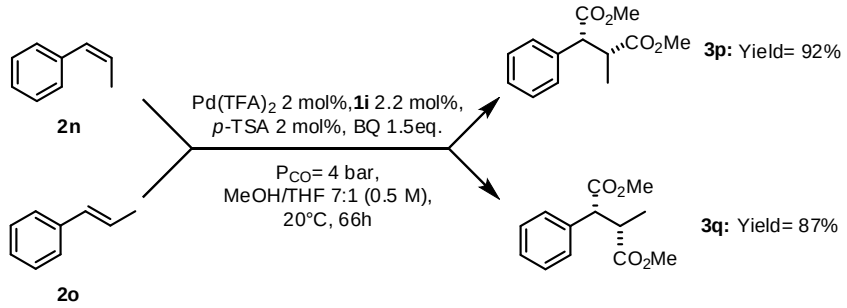
Halogens were quite well tolerated in the methoxycarbonylation reaction producing esters **3e**, **3f**, and **3i** with excellent yields (Table 7, entries 5, 6 and 9, respectively). Although vinyl arenes **2g** and **2h**, bearing *o*-Cl and *o*-Br substituents, respectively were fairly converted, the selectivity was utterly complete (Table 7, entries 7 and 8).

Vinyl naphtalene and aliphatic olefins, such as 1-heptene **2k** and 1-(but-3-enyl)benzene **2l,** were in general less reactive and a slight increase of catalyst loading (up to 1 mol%) were needed to achieve excellent results in term of isolated yield and selectivity (Table 7, entries 10–12), and succinic acid esters **3j–l** were isolated with 77–92 % yields.

Even with an aliphatic olefin hindered in alpha position, such as 3,3-dimethyl-1-butene **2m**, the carbonylated product **3m** was obtained with 95% yield over a converted starting material of 53% (Table 7, entry 13), with 2 mol% of catalyst loading.

A survey of different alcohols as nucleophiles in place of methanol was made to prove the broadness of the methodology and to synthesize different products with orthogonal cleavable *i*-propyl- and benzyl- ester groups (**3n–o**), very useful in synthetic organic and medicinal chemistry (Table 7, entries 14–15). Isopropanol and benzyl alcohol were reactive enough to cause complete styrene conversion, even though with a higher catalyst loading (2 mol% of $Pd(TFA)_2$/**1i**; Table 7, entries 14 and 15).

Regarding internal olefins, while no reaction occurred using the initial reaction conditions reported in Table 2, the carbonylation carried out with $Pd(TFA)_2$/**1i** (2 mol%) allowed a complete conversion of *cis*- and *trans*-β-methylstyrene (Scheme 47).



Scheme 47. Bis-alkoxycarbonylation reaction with 1,2-disubstituted olefins 2n and 2o.

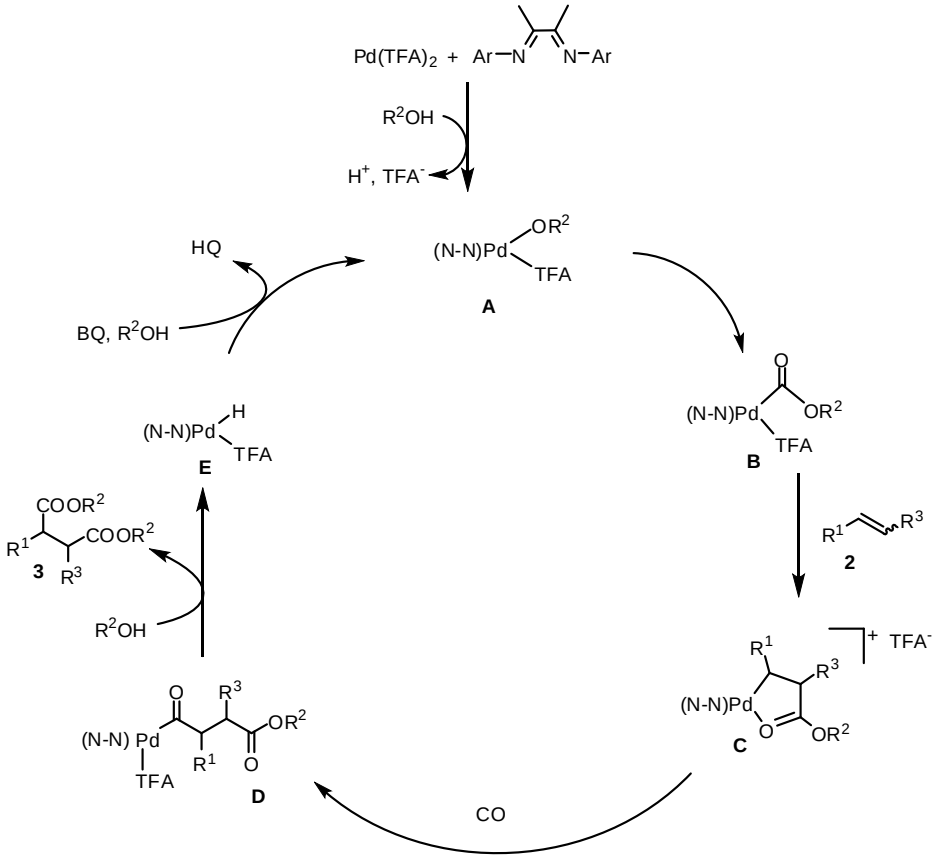
The resulting products **3p** and **3q** were obtained in good isolated yields of 92% and 87% respectively, with total diastereoselectivity (Scheme 47). The geometry of compounds **3p** and **3q** comes from a *syn* overall addition of the carboxyl moieties to the olefin.[111] This reaction, in agreement with a generally accepted mechanism, passes through a concerted *syn* addition of the Pd-carbonyl fragment of the catalyst to the olefin double bond, via a four-membered transition state.[112]

According to the above results and the literature data,[101, 108, 112] we can speculate on the mechanism of the reaction. As depicted in Scheme 48, the first step of the process is the formation of the active species **A** (Scheme 48) from the reaction of $Pd(TFA)_2$ with the DAB ligands and the alcohol. Ancillary experiments were conducted to support the proposed catalytic cycle. Ligand **1i** was added to a THF solution of $Pd(TFA)_2$ and benzoquinone, to avoid a relatively fast decomposition. After removing the solvent from the reaction mixture, the ^1H NMR, recorded in $CDCl_3$, showed signals attributable to the precatalyst $[(N–N)Pd(THF)_2]^{2+}[TFA^-]_2$. Unfortunately the addition of methanol produced an immediate decomposition of the complex to palladium black. Hereafter, insertion of CO in complex A gives the alkoxycarbonylpalladium complex **B**, followed by the insertion of the alkene **2**. The 5-membered palladacycle intermediate **C** (Scheme 48) is the result complex, [108] however

[111] Aratani, T.; Tahara, K.; Takeuchi, S.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2007**, *36*, 1328.

[112] a) Carfagna, C.; Gatti, G.; Mosca, L.; Natanti, P.; Paoli, P.; Rossi, P.; Gabriele, B.; Salerno, G. *Dalton Trans.* **2011**, *40*, 6792. b) Carfagna, C.; Gatti, G.; Mosca, L.; Paoli, P.; Guerri, A. *Helv. Chim. Acta* **2006**, *89*, 1660.

formation of an η^3-allylic intermediate in equilibrium with **C**, cannot be ruled out.[106] In any case, further CO insertion to give complex **D** followed by nucleophilic displacement by the alcohol, leads to the final product **3** (Scheme 48) and palladium hydride complex **E**. Finally, the presence of benzoquinone regenerates the active species **A** (Scheme 48) thus closing the catalytic cycle.[110]



Scheme 48. Proposed catalytic cycle for the oxidative carbonylation of alkenes.

The main parameters that influence our bis-alkoxycarbonylation method are: the type of ligand, the presence of *p*-TSA together with the ROH/THF ratio. While the last parameter mainly affects the ratio of compounds **3a**/**4a**, the roles played by the *p*-TSA and the ligand are more complex. First of all, the sulphonic acid increases the **3a**/**4a** ratio and enhances the catalytic efficiency (TON and TOF). In particular, *p*-TSA can decrease the amount of the phenate anion in equilibrium with hydroquinone, suppressing the formation of product **4a**. Moreover, as reported by Bianchini et al.,[101] the lack of formation of palladium black can be related to the acid stabilization of the intermediate complex **E** (Scheme 48) that improves the oxidizing ability of BQ.

Regarding the ligand, catalytic species formed from ligands bearing *ortho*-disubstituted aryl rings, such as **1f** and **1i**, show to be more active than the other ones. This is probably due to the particular conformation of the *in situ* formed complexes. In fact, with ligands **1f** and **1i**, strong steric interactions between the substituents of the diimine backbones and the phenyl rings constrain the aryls to arrange almost perpendicularly with respect to the palladium mean

coordination plane.[106] This conformation affects the coordination of the aromatic olefin making possible a π-stacking interaction in the olefin insertion transition states that could be the origin for the high productivity found both in the CO/vinylarene copolymerization[106] and in the bis-alkoxycarbonylation reaction reported here. With the *ortho*-disubstituted aryl ligand **1e** the reaction still carried out but the conversion was not satisfactory (70%, Table 2 entry 6) probably due to the highly bulky isopropyl groups on the aryls which cause a difficult access of the olefin and CO to the catalytic center.[106] Conversely the right size to promote the reaction to completion is present with $Pd(TFA)_2$/**1f** catalyst system, with the methyl groups on the aryls, but the selectivity towards MeOH or HQ, to achieve **3a**:**4a** in good ratio, is still lacking (Table 2 entry 7 and 10).[106] Finally the complete conversion and selectivity observed in the bis-alkoxycarbonylation reaction with $Pd(TFA)_2$/**1i** catalyst (Table 5, entry 1) can be assigned to the precise steric hindrance of the anthryl moieties and to a greater ability of complex **D** to undergo alcoholysis by ROH rather than cleavage by hydroquinone (Scheme 48)

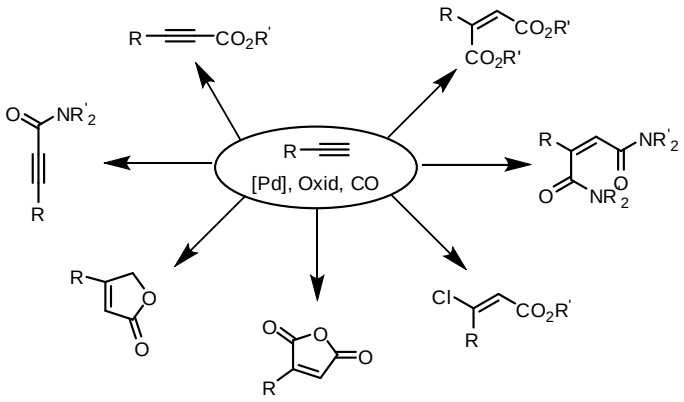
In conclusion, we have developed an efficient method for the Pd catalyzed bis-alkoxycarbonylation of olefins **2** to give succinic diesters **3** in good yields and high selectivity, under particularly mild reaction conditions (4 bar of CO at 20° C). Variously substituted aryl α-diimine ligands have been used for the first time in this kind of reaction, together with $Pd(TFA)_2$ as palladium source, alcohols as nucleophiles and 1,4-benzoquinone as oxidant.

In conclusion, we have provided a new contribution to the Pd-catalyzed bis-alkoxycarbonylation of olefins by applying to the reaction, for the first time, variously substituted aryl α-diimine ligands. In particular, a very simple catalytic system, synthesized *in situ* from the 9-antryl ligand **1i** and $Pd(TFA)_2$, was used for the highly selective quantitative conversion of olefins to succinic acid esters in excellent yields, with low catalyst loading. The optimized reaction proofed to be very general, in fact it was applicable not only with aromatic and aliphatic olefins but also with different alcohols as reagents, under mild conditions. Considering the data collected in this manuscript and the past contribution of our group we have postulated a more than probable mechanism. Regarding the internal olefins, the oxidative carbonylation allowed a complete conversion of *cis* and *trans*-β-methylstyrene into a bis-carbonylated product with total diastereoselectivity.

6. Oxidative Alkoxycarbonylation of Alkynes

6.1 Introduction

The palladium-catalyzed oxidative carbonylation of the alkynes is common to give a mixture of a product, nevertheless these reactions can be interesting due to the tunability any the ability to convert raw material such as alkynes with carbon monoxide in highly valuable building block in organic and medicinal chemistry (Scheme 49).[45,94a,113]



Scheme 49. Palladium-catalyzed oxidative carbonylation of alkynes.

Propiolic acid and their derivatives are very important compound in organic synthesis[114] and a useful building bock in pharmaceutical and medicinal chemistry.[115] As an example, laulimalide analogues were reported in 2004 and one of this have a propiolate fragment in its chemical structure (Figure 7). Laulimalide is a potent, structurally unique microtubule-stabilizing agent originally isolated from the marine sponge *Cacospongia mycofijiensis* that promotes abnormal tubulin polymerization and apoptosis in vitro, with a similar mode of action to of Taxol, but with potentially less susceptibility to multidrug resistance.

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[113] a) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825; d) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788. b) Liu, J.; Chen, J.; Sun, W.; Xia, C. *Chin. J. Catal.* **2010**, *31*, 1; c) Brennfuehrer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28; d) Brennfuehrer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114; e) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402-5422; i) Gabriele, B.; Salerno, G.; Costa, M. *Top. Organomet. Chem.* **2006**, *18*, 239. f) Godard, C.; Muñoz, B. K.; Ruiz, A.; Claver, C. *Dalton Trans.* **2008**, 853.

[114] a) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111; b) Jacobsen, M. J.; Funder, E. D.; Cramer, J. R.; Gothelf, K. V. *Org. Lett.* **2011**, *13*, 3418; c) Meng, L.-G.; Ge, N.-L.; Yang, M.-M.; Wang, L. *Eur. J. Org. Chem.* **2011**, 3403; d) Bararjanian, M.; Balalaie, S.; Rominger, F.; Movassaghi, B.; Bijanzadeh, H. R. *J. Org. Chem.* **2010**, *75*, 2806; e) Trost, B. M.; Toste, F. D.; Greenma, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518; f) Pattenden, G.; Tankard, M. *Tetrahedron Lett.* **1993**, *34*, 2677; g) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. *J. Org. Chem.* **1998**, *63*, 5050.

[115] a) Mooberry, S. L.; RandallHlubek, D. A.; Leal, R. M.; Hegde, S. G.; Hubbard, R. D.; Zhang, L.; Wender, P. A. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 8803; b) Setoh, M.; Yamada, O.; Ogasawara, K. *Heterocycles* 1995, 40, 539–542; c) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B.*Tetrahedron* **1988**, *44*, 481–490; d) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1987**, *28*, 1857–1860.

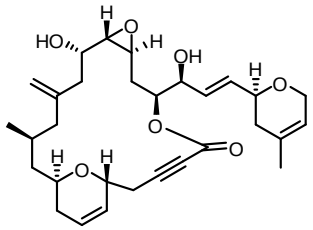
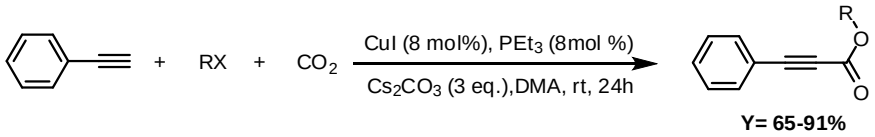


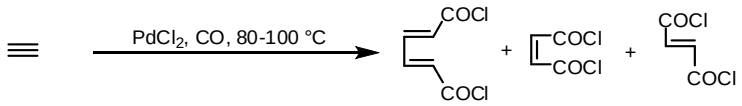
Figure 7. Propiolic esters C2-C3 of Laulimalide: synthetic analogue.

The propiolic esters are traditionally synthesized lithiating the C_{sp}-H moiety and quenching it with C1 synthetic equivalent such as a chloroformate or carbon dioxide however reaction conditions are quite harsh as a strong base is required, drastically reducing functional groups compatibility. Recently, different contributions have appeared in the literature featuring a copper- and silver-mediating carboxylation of different alkynes with carbon dioxide.[116] A variety of functionalized alkyl 2-alkynoates can be achieved under ambient conditions using a copper/phosphine catalyst system starting from terminal alkynes and CO_2 in the presence of alkyl halides (Scheme 50).[116c]

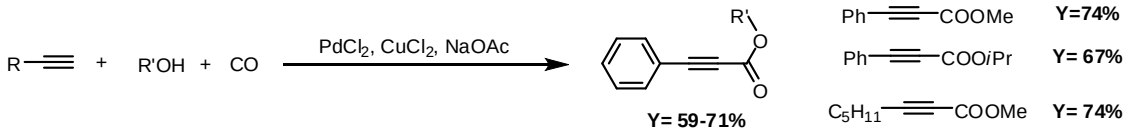


Scheme 50. Carboxylation of terminal alkynes promoted by copper(I) catalyst.

Another approach to the synthesis of propiolic acid derivatives is performed by using carbon monoxide as cheap feedstock under oxidative conditions. The reaction was first introduced by Tsuji and co-workers in 1964, converting the acetylene into muconyl and maleic acid chloride with a stoichiometric amount of $PdCl_2$ (Scheme 51),[48a] and later the authors synthesized propiolic acid esters using 5 mol% of $PdCl_2$ in combination with $CuCl_2/O_2$ system as the oxidant to close the catalytic cycle (Scheme 52).[48a]



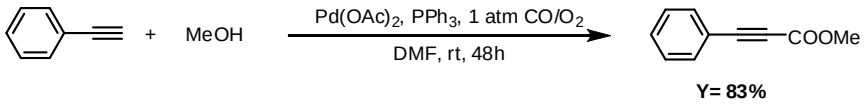
Scheme 51. Oxidative carbonylation promoted by a stoichiometric amount of $PdCl_2$.



Scheme 52. Palladium-catalyzed oxidative carbonylation.

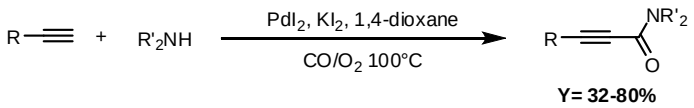
[116] a) Yu, D.; Zhang, Y. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20184; b) Gooßen, L. J.; Rodríguez, N.; Manjolinho, F.; Lange, P. P. *Adv. Synth. Catal.* **2010**, *352*, 2913.c) Inamoto, K.; Asano, N.; Kobayashu, K.; Yonemoto, M.; Kondo, Y. *Org. Biomol. Chem*. **2012**, 10, 1514-1516.

During the last four decades various methodologies for the synthesis of 2-ynoates and 2-ynamides have been developed and most of them involving the use of a Pd(II) catalyst and oxygen.[57b,58,117] In 2004, Yamamoto and co-workers reported the mono-alkoxycarbonylation of 1-alkynes to produce alkyl 2-alkynoates using palladium/phosphine catalyst and molecular oxygen as an oxidant at room temperature and one atmosphere of CO (Scheme 53).[57b]



Scheme 53. Alkoxycarbonylation of 1-alkynes using O_2 as oxidant.

While 2-ynamides, a useful intermediates for the synthesis of many biologically active molecules and heterocyclic compounds,[118] can be synthesized by direct amminocarbonylation of alk-1-ynes. The first example of catalytic amminocarbonylation both alkyl- and arylacetylenes was reported by Gabriele and co-workers (Scheme 54). Alkynes are converted into 2-ynamides and with alkylacetylenes, as a substrates, also generated small amounts of by-product resulting from oxidative diaminocarbonylation of the triple bond. In addiction the best result was achieved by using of nucleophilic secondary ammine meanwhile the reaction of primary amines led to complex reaction mixtures.[117]



Scheme 54.Oxidative aminocarbonylation of alk-1-ynes.

This methodology has been successfully applied to the direct synthesis of a variety of carbonylated heterocycles starting from terminal alkynes bearing a suitably placed nucleophilic group.[119]

Alkynes can be carbonylated not only to propiolic acid derivatives but also to a variety of different compounds such as maleic and fumaric acid derivatives,[120] halo-[121] and unsaturated lactones.[119a,b,122] Another useful product, that is possible to obtain from alkyne by oxidative

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[117] Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, *622*, 84.

[118] a) Pattenden, G.; Tankard, M. *Tetrahedron Lett.* **1993**, *34*, 2677. b) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. *J. Org. Chem.* **1998**, *63*, 5050 – 5058.

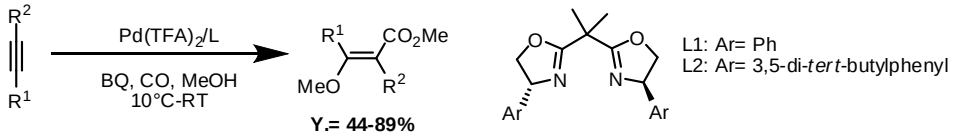
[119] a) Gabriele, B.; Salerno, G.; Plastina, P.; Costa, M.; Crispini, A. *Adv. Synth. Catal*. **2004**, *346*, 351. b) Gabriele, B.; Salerno, G.; Plastina, P. *Lett. Org. Chem*. **2004**, *1*, 134. c) Gabriele, B.; Plastina, P.; Salerno, G.; Costa, M. *Synlett* **2005**, 935. d) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319 e) Gabriele, B.; Salerno, G.; Veltri, L.; Mancuso, R.; Li, Z.; Crispini, A.; Bellusci, A. *J. Org. Chem.* **2006**, *71*, 7895.

[120]a) Sakurai, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Letters* **1999**, *40*, 1701. b) Alper, H.; Despeyroux, B.; Woell, J. B. *Tetrahedron Lett.* **1983**, *24*, 5691. c) Giannoccaro, P.; Aresta, M.; Doronzo, S.; Ferragina, C. *Appl. Organomet. Chem.* **2000**, *14*, 581. d) Zargarian, D.; Alper H. *Organometallics* **1991**, *10*, 2914. e) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Chem. Commun.* **1999**, 138. f) Li, J.; Li, G.; Jiang, H.; Chen, M. *Tetrahedron Lett.* **2001**, *42*, 6923.

[121] a) Li, J.; Jiang, H.; Feng, A.; Jia, L. *J. Org. Chem.* **1999**, *64*, 5984; b) J.-H. Li, S. Tang, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 477;

[122] Carfagna, C.; Gatti, G.; Mosca, L.; Paoli, P.; Guerri, A. *Chem. Eur. J.* **2005**, *11*, 3268.

carbonylation reaction, is the alkoxy-acrylate.[123] One of the most recent example is reported by Kato and co-workers in 2009 where alkynes is converted into β-methoxyacrylates in good yields (Scheme 55) with a good tolerance towards to acetyl, ketal, and free hydroxyl and acid-sensitive glycosidic groups. The reaction is promoted by Pd/bis(oxazoline) complexes and the benzoquinone acted as a organic oxidant.[124]



Scheme 55. Palladium-catalyzed oxidative carbonylation of alkynes.

Despite the massive amount of work done up until now the oxidative carbonylation of alkynes still lacks broadness of substrates and different reaction conditions are necessary depending from the substrates, the alcohols and the catalysts employed. Moreover generally high catalyst loadings are required to bring the reaction to completion. Based on the development of a very appealing catalytic system, consisting of a palladium source with aryl-α-diimine ligands for the carbonylation of olefins to succinic acid ester with high selelctivity and efficiency.[125] In this regard we set out to transfer the effectiveness of the abovementioned [Pd]/diimine catalytic system to the carbonylation of terminal and internal alkynes.

[123] a) Okumoto, H.; Nishihara, S.; Nakagawa, H.; Suzuki, A. *Synlett* **2000**, 217; b) Marshall, J. A.; Yanik, M. M.; *Tetrahedron Lett.* **2000**, *41*, 4717; c) Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* **2003**, *5*, 4429; d) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203. e) Kato, K.; Matsuba, C.; Kusakabe, T.; Takayama, H.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Tetrahedron* **2006**, *62*, 9988. f) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 4915; g) Miyakoshi, N.; Mukai, C. *Org. Lett.* **2003**, 5, 2335.
[124] Kato, K.; Motodate, S.; Mochida, T.; Kobayashi, T.; Akita, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3326.
[125] Fini, F.; Beltrani, M.; Mancuso, R.; Gabriele, B.; Carfagna, C. *Adv. Synth. Catal.* **2015**, *357*, 177–184.

6.2 Results and discussion

6.2.1 Oxidative Carbonylation on Alkynes: Screening of α-diimine Ligands and Reaction Conditions.

To begin with, an extensive work of optimization has been carried out testing common source of palladium, such as $Pd(TFA)_2$ and $(PhCN)_2PdCl_2$ and aryl α-diimine ligands (Figure 8).

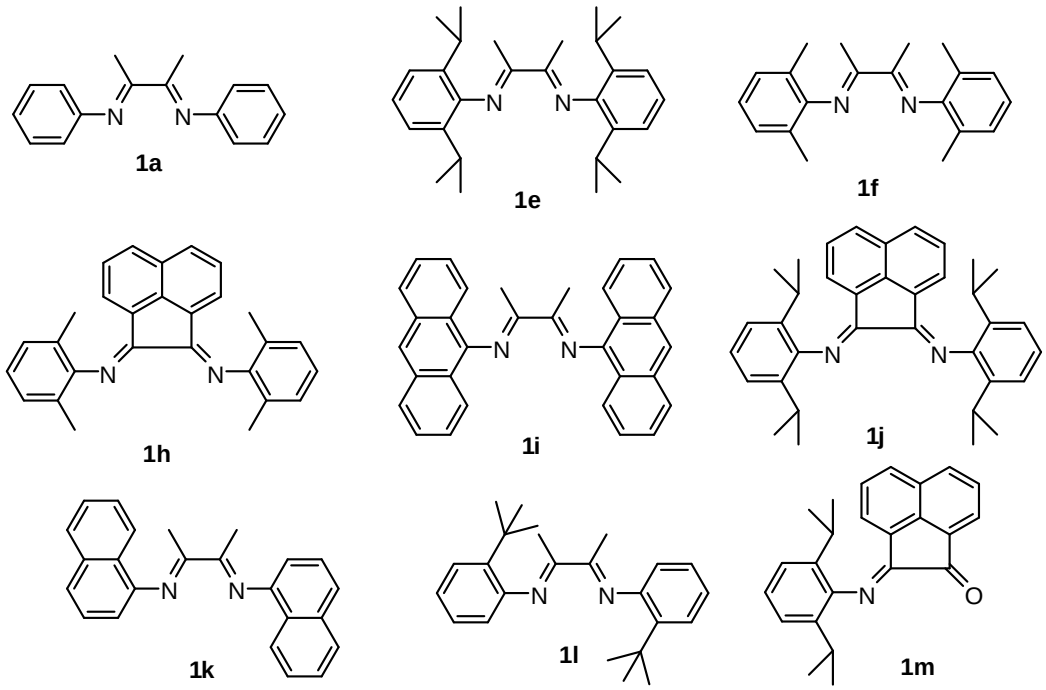
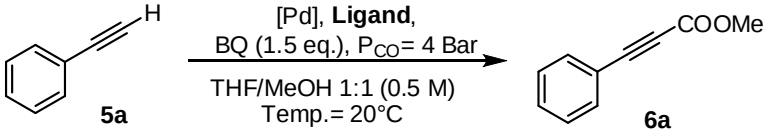


Figure 8. Aryl α-diimine ligands tested in the reaction optimization process.

The initial reaction conditions were as close as possible to the previously reported bis-alkoxycarbonylation of olefins,[125] consisting of mild conditions in terms of CO pressure (4 bar) and temperature (20°C), using THF/MeOH mixture as solvent and benzoquinone (BQ, 1.5 eq.) as the oxidizing agent. The carbonylation of phenylacetylene with 5 mol% of $Pd(TFA)_2$/**1f** catalytic system afford no conversion whatsoever, proving that alkynes are quite unreactive compared with olefins (Table 8, entry 1). At this point a highly reactive catalytic specie $(PhCN)_2Pd(OTf)_2$/**1f** *in situ* generated from $(PhCN)_2PdCl_2$, 2 eq. of AgOTf and ligand **1f**, were introduced. This catalytic system was very effective and the phenylacetylene **5a** was converted for 80% towards phenylpropiolic acid methyl ester **6a** by using just 0.5 mol% of catalyst loading, in 48 h (Table 8, entry 2).

Table 8.Optimization of the oxidative carbonylation of the phenylacetylene.



Entry[a)]	[Pd] (mol%)	**Ligand** (mol%)	Additive (mol%)	Conv. (%)[b)]
1	$Pd(TFA)_2$ (5)	**1f** (5.5)	--	<5%
2	$(PhCN)_2PdCl_2$ (0.5)	**1f** (0.55)	AgOTf (1.1)	80
3	$(PhCN)_2PdCl_2$ (0.5)	--	AgOTf (1.1)	55%
4	$(PhCN)_2PdCl_2$ (0.5)	**1f** (0.55)	--	<5%
5	--	**1f** (0.55)	AgOTf (1.1)	<5%
6	$(PhCN)_2PdCl_2$ (0.5)	**1f** (0.55)	$AgPF_6$ (1.1)	10%
7	$(PhCN)_2PdCl_2$ (0.5)	**1f** (0.55)	$AgSO_3CH_3$ (1.1)	70%
8[c)]	$(PhCN)_2PdCl_2$ (0.5)	**1f** (0.55)	AgOTf (1.12)	40%
9[d)]	$(PhCN)_2PdCl_2$ (0.5)	**1f** (0.55)	AgOTf (1.1)	80%
10	$(PhCN)_2PdCl_2$ (0.5)	**1i** (0.55)	AgOTf (1.1)	45%
11	$(PhCN)_2PdCl_2$ (0.5)	**1e** (0.55)	AgOTf (1.1)	>95%
12	$(PhCN)_2PdCl_2$ (0.5)	**1h** (0.55)	AgOTf (1.1)	30%
13	$(PhCN)_2PdCl_2$ (0.5)	**1j** (0.55)	AgOTf (1.1)	>95%
14	$(PhCN)_2PdCl_2$ (0.1)	**1e** (0.11)	AgOTf (0.22)	25%
15	$(PhCN)_2PdCl_2$ (0.1)	**1j** (0.11)	AgOTf (0.22)	80%
16[e)]	$(PhCN)_2PdCl_2$ (0.5)	**1j** (0.55)	AgOTf (1.1)	65%
17[f)]	$(PhCN)_2PdCl_2$ (2)	**1j** (2.2)	AgOTf (4.5)	>95%

a) Reaction performed in autoclave at P_{CO} = 4 bar, with phenylacetylene **5a** (2 mmol-scale), Pd(II) 5 mol%, 0.5 mol% or 0.1 mol% (0.10, 0.01 mmol or 0.002 mmol), **ligands** 5.5 mol%, 0.55 mol% or 0.11 mol% (0.11 mmol, 0.011 mmol or 0.0022 mmol), Ag(I) 1.1 mol% or 0.22 mol% (0.022 or 0.0044 mmol) and the 1.5 eq of BQ (3 mmol) with THF/MeOH 1:1 (0.5 M) as reaction medium at 20°C, for 42 h.

b) Determined by direct ^{1}H NMR analysis of a sample of the reaction mixture.

c) Reaction performed at 8 bar of CO.

d) Reaction performed at 60°C.

e)Reaction performed in a Schlenk tube at atmospheric pressure of CO (balloon).

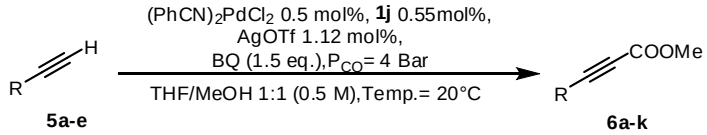
f) Reaction performed in a Schlenk tube at atmospheric pressure of CO (balloon) with **5a** (2 mmol), $(PhCN)_2PdCl_2$ 2 mol% (0.04 mmol), ligand **1j** 2.2 mol% (0.044 mmol) and AgOTf 4.5 mol% (0.09 mmol) with the stated time, oxidant and temperature

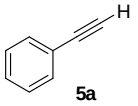
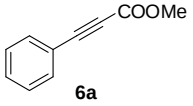
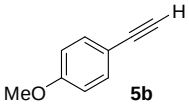
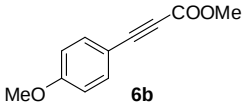
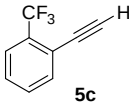
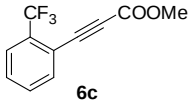
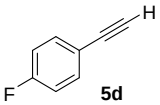
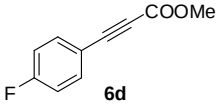
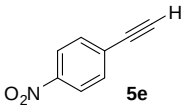
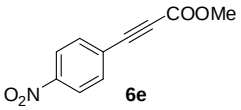
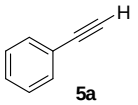
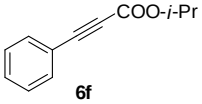
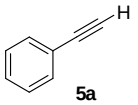
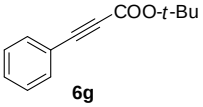
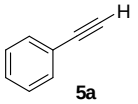
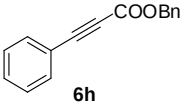
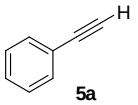
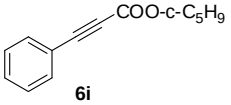
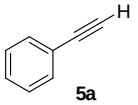
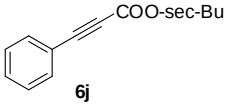
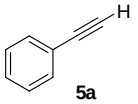
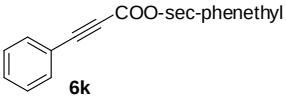
The catalytic system was proved to be consistent, performing the reaction without the ligand only 55% of conversion has been obtained (Table 8, entry 3). Moreover running the reaction without AgOTf or without the source of palladium the system was unreactive toward **5a** (Table 8, entries 4 and 5). Subsequently both the silver salt and reaction conditions were varied. Unfortunately neither $AgPF_6$ nor $AgSO_3CH_3$ changed the efficiency of the process and by increasing the temperature to 60°C (Table 8, entries 6, 7) and the pressure of CO to 8 bar no beneficial effect was provided (Table 8, entries 8, 9). At this point, an optimization of the ligand was taken into consideration (Table 8, entries 10-13). First ligand **1i** was tested, but despite being the best ligand for the bis-alkoxycarbonylation of olefins,[125] it did not fitted for the mono-alkoxycarbonylation of alkynes (Table 8, entry 10). Conversely **1e** and **1j** resulted to be quite effective, bringing the reaction to completion probably due to the high steric hindrance on the *ortho* positions of the aryl moiety (Table 8, entries 11 and 13). At last the catalytic system in situ synthesized with ligand **1h** was poorly active (Table 8, entry 12). By lowering the catalyst loading down to 0.1 mol% (S/C 1000:1), the efficiency of the process was further tested with both the best ligands **1e** and **1j** (Table 8, entries 14 and 15). In these cases the two results were quite different and only the catalytic specie bearing the bis(2,6-diisopropyl)-acenaphthenequinonediimine (diaryl-BIAN) **1j** retained most of its activity converting phenylacetylene **5a** for 80% with a TON up to 800 and TOF of 9.5 h^{-1}, maintaining complete selectivity toward phenylpropiolic acid methyl ester **6a** (Table 8, entry 15). Finally by performing the mono-alkoxycarbonylation of phenylacetylene at atmospheric pressure of CO a certain degree of reactivity was preserved by using 0.5 mol% of catalyst loading (S/C 200:1) (conv. 65%, Table 8, entry 16), meanwhile complete conversion of the starting material was achieved, by slightly increasing the loading of the in situ synthesized $(PhCN)_2Pd(OTf)_2$/**1j**, up to 2 mol% (Table 8, entry 17).
In conclusion, not only the system is highly efficient at mild reaction condition such as 4 bar of carbon monoxide and room temperature, but also at atmospheric pressure of CO, allowing the use of simple Schlenk tube equipped with a balloon as a reservoir of CO (Table 8, entries 16-17).

6.2.2 Oxidative Carbonylation on Alkynes: Substrates Scope

With these data in hand we extended the process to several aromatic and alkynes by performing the reaction with conditions able to guarantee full conversion of substrates **5**, such as 0.5 mol% of catalyst loading and 4 bar of CO at 20°C (Table 9). The bis(2,6-diisopropylphenyl)imino]acenaphthene ligand **1j** that give the best result for the mono-alkoxycabonylation of acetylenes, was synthesized by condensation reaction acid catalyzed between acenaphthenequinone and 2,6-diisopropylaniline in acetonitrile under reflux, according with the procedure previously reported in literature.[109a]

Table 9. Substrate scope of the mono-alkoxycarbonylation of alkynes 5a-e



Entry[a)]	Alkynes **5a-e**	Products **6a-k**	Yields (%)[b)]
1	 **5a**	 **6a**	90
2	 **5b**	 **6b**	82
3	 **5c**	 **6c**	53
4	 **5d**	 **6d**	71
5[c)]	 **5e**	 **6e**	31
6	 **5a**	 **6f**	92
7	 **5a**	 **6g**	73
8	 **5a**	 **6h**	75
9[d)]	 **5a**	 **6i**	75
10	 **5a**	 **6j**	60
11	 **5a**	 **6k**	56

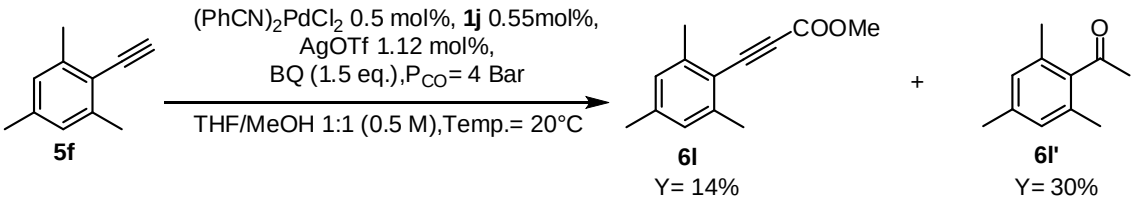
a) Reaction performed in autoclave at P_{CO} =4 bar, with alkynes **5a-e** (2 mmol-scale), $(PhCN)_2PdCl_2$ 0.5 mol% (0.01 mmol), ligand **1j** 0.55 mol% (0.011 mmol), AgOTf 1.1 mol% (0.022 mmol) and 1.5 eq of BQ (3 mmol) with THF/MeOH 1:1 (0.5 M) as reaction medium at 20°C, for 42 h.

b) Isolated yields after column chromatography.

c) Reaction performed with 2 mol% catalyst loading.

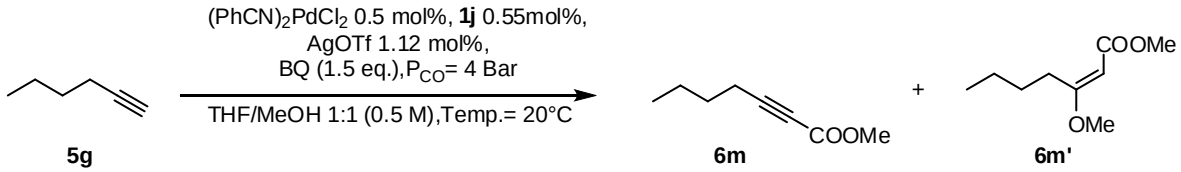
d) Reaction performed with 2 mol% catalyst loading, using cyclopentanol in place of methanol.

Good to excellent results were obtained in term of isolated yields, the best outcome was achieved with phenylacetylene **5a**, affording **6a** with excellent isolated yields (90%, Table 9, entry 1). Phenylacetylene **5b–5d** bearing electron donating or electron withdrawing groups were compatible with the catalytic system even in the presence of halogens (Table 9, entries 2–4), as a matter of fact products **6b–6d** were attained with moderate to good isolated yields (53–82%, Table 9, entries 2–4). Even with strong electron–withdrawing group such as nitro group in para position (**5e**) the system was still active. By using a catalyst loading of 2 mol%, the process gave a mono-alkoxycarbonylation product with a isolated yield of **6e** of 31% (Table 9, entry 5). During the substrate scope, 2-ethynyl-1,3,5-trimethylbenzene **5f** was then tested to prove the efficiency of the system toward sterically hindered starting material. Despite a slightly lower conversion (85 %), the catalyst maintained most of its activity but it lost its selectivity and together with the corresponding phenylpropiolic acid methyl ester **6l** a byproduct was isolated 1-mesitylethanone **6l'**(Scheme 56).



Scheme 56. Mono-alkoxycarbonylation of 2-Ethynyl-1,3,5-trimethylbenzene 5f.

Together with aromatic alkynes, an aliphatic alkynes as hex-1-yne **5g** was examined to broaden the scope of the reaction (Scheme 57). Unfortunately, despite a highly conversion of aliphatic alkenes the mono-alkoxycarbonylated product **6m** and β-methoxy acrylate [(E)-methyl 3-methoxyhept-2-enoate] **6m'** was isolated with low yields and characterized in accordingly to the carbonylation reported by Kato and co-workers in 2009.[124] This result could be associate to the low boling temperature of the products



Scheme 57. Mono-alkoxycarbonylation of hex-1-yne 5g.

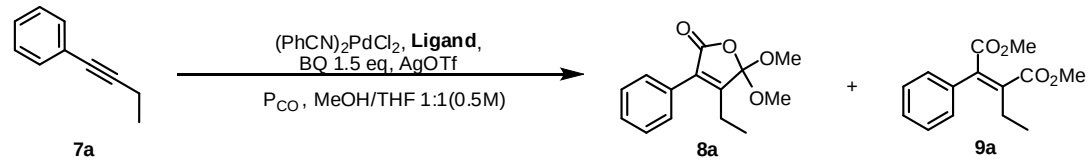
Finally by using phenylacetylene **5a** a survey of different alcohols was performed (Table 9, entry 6–11). Good to excellent results in term of isolated yield were obtained, from a less–hindered alcohol such as benzyl alcohol (Table 9, entry 8), passing through secondary alcohols as isopropanol, cyclopentanol, *sec*-butanol, and *sec*-phenethanol (Table 9, entries 6, 9–11), to the more–hindered *tert*-butanol (Table 9, entry 7), proving that the system well tolerate different alcohols as the nucleophile.

In conclusion a range of several alkynes and various alcohols were tested in the mono-alkoxycarbonylation of terminal triple bond proving the selectivity, the generality and the efficiency of the reaction.

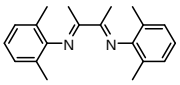
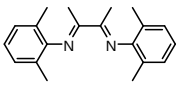
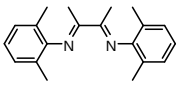
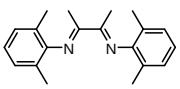
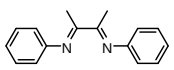
6.2.3 Oxidative Carbonylation on 1,2-Disubstituted Alkynes

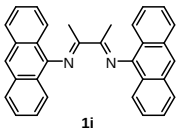
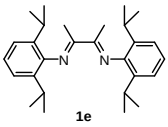
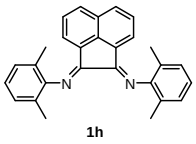
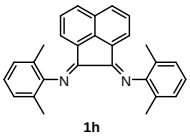
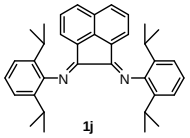
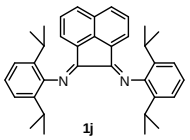
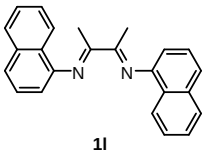
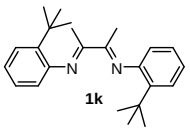
Stimulated by these results we went further to explore the 1,2-disubstituted alkynes. As before we choose a substrate as the model to study and eventually optimize the carbonylation reaction. 1-phenyl-1-butyne **7a** was the reagent of choice, inexpensive and readily available from several chemical suppliers (Table 10). The reaction is performed with a catalyst system formed *in situ* from $(PhCN)_2PdCl_2$ and DAB ligand in the presence of benzoquinone as the oxidant in MeOH/THF mixture as solvent.

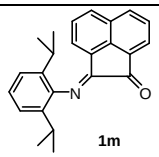
Table 10. Bis-methoxycarbonylation of 1-phenyl-1-butyne 7a catalyzed by $(PhCN)_2PdCl_2$ with DAB ligands.



7a **8a** **9a**

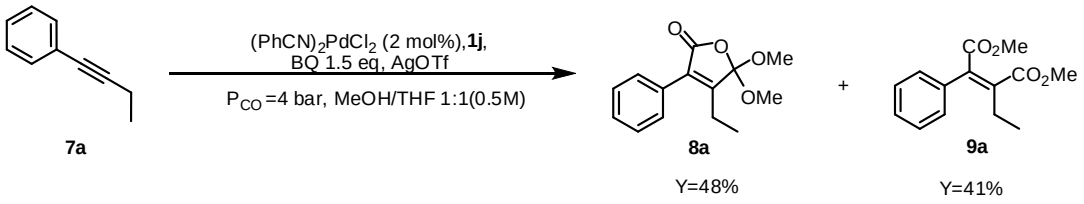
Entry[a]	**Ligand**	Additive (mol%)	P_{CO} (bar)	T (°C)	Conv. (%)[b]	**8a:9a** ratio[b]
1[c]	-	AgOTf 4,5	1	19°C	<5%	--
2[c]	 **1f** 2,2 mol%	AgOTf 4,5	1	19°C	40%	20%:20%
3	-	AgOTf 4,5	4	19°C	<5%	--
4	 **1f** 2,2 mol%	AgOTf 4,5	4	19°C	80%	54%:26%
5	 **1f** 2,2 mol%	AgOTf 4,5 *p*-TSA 4%	4	19°C	66%	41%:25%
6	 **1f** 2,2 mol%	AgOTf 4,5	8	60°C	98%	47%:39%
7	 **1a** 2,2 mol%	AgOTf 4,5	4	19°C	<5%	--

8	 1i 2,2 mol%	AgOTf 4,5	4	20°C	83%	41%:42%
9	 1e 2,2 mol%	AgOTf 4,5	4	19°C	87%	40%:47%
10	 1h 2,2 mol%	AgOTf 4,5	4	19°C	82%	55%:27%
11	 1h 2,2 mol%	AgOTf 4,5	8	20°C	98%	57%:41%
12	 1j 2,2 mol%	AgOTf 4,5	4	19°C	98%	56%:42%
13	 1j 0,55 mol%	AgOTf 1,12	4	20°C	44%	24%:21%
14	 1l 2,2 mol%	AgOTf 4,5	4	19°C	49%	27%:22%
15	 1k 2,2 mol%	AgOTf 4,5	4	19°C	54%	32%:22%

16	 1m 2,2 mol%	AgOTf 4,5	4	22°C	67%	45%:22%

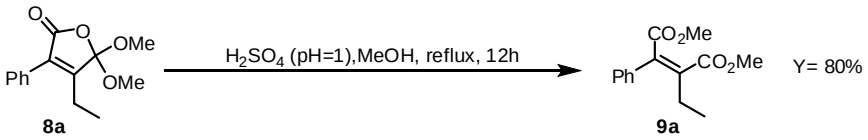
a) Reaction performed in autoclave at rt, with phenylacetylene **7a** (2 mmol-scale), Pd (II) 2 mol% or 0.5 mol% (0.04, 0.01mmol), **ligands** 2.2 mol% or 0.55 mol% (0.044, 0.011mmol) and the 1.5 eq of BQ (3 mmol) with THF/MeOH 1:1 (0.5 M) as reaction medium for 42 h.
b) Determined by direct ^{1}H NMR analysis of a sample of the reaction mixture.
c) Reaction performed in a Schlenk tube at atmospheric pressure of CO (balloon).

While no reaction took place in the absence of ligands both at atmospheric pressure of CO (Table 10, entry 1) and at 4 bar of carbon monoxide (Table 10, entry 3), the use of the ligand with *ortho*-disubstituted-diaryl DAB ligand bearing methyl groups on the aromatic rings **1f,** total conversions of 1-phenyl-1-butyne were attained with a carbon monoxide pressure of 8 bar (Table 10, entry 5), meanwhile at 19°C and lesser pressure of CO the system was not efficient (Table 10, entries 2 and 4). 1-phenyl-1-butyne was converted, for the first time, into a 4-ethyl-5,5-dimethoxy-3-phenylfuran-2(5H)-one **8a** and dimethyl 2-ethyl-3-phenylmaleate **9a**, two products derived from the bis-alcoxycarbonylation reaction of the substrates. Even the presence of the *p*-TSA was gave no beneficial effect to the bis-carbonylation of the alkynes **7a** (Table 10, entry 5).
Using another ligand with bulky isopropyl groups in the *ortho* position of the aromatic rings **1e** and bis(9-anthryl)-2,3-dimethyl-1,4-diazabutadiene **1i** high conversion (83%-87%) was obtained at mild reaction condition with pressure of carbon monoxide of 4 bar at 20 °C (Table 10, entry 8 and 9). Of paramount importance is the presence of *ortho*-disubstituted-diaryl on the aryl ring of the α-diimine ligand is for the bis-alcoxycarbonylation reaction as a matter of fact the catalyst system formed by $(PhCN)_2Pd(OTf)_2$ and the ligand **1a**, without any substitution in ortho position, was no active (Table 10, entry 7).
Passing from the ligand **1e** to **1j**, bearing acenaphthene backbones with bulky isopropyl groups in the *ortho* position, the best result in term of conversion was achieved as complete conversion of 1-phenyl-1-butyne into bis-carbonylated products at mild reaction condition (Table 10, entry 12).
The carbonylation reaction is poorly selective and the two products are formed in different proportions. Moreover different asymmetrical aryl α-diimine ligands **1k**, **1l**, **1m** were tested but unfortunately no beneficial effect were noted in term of reagent conversion (Table 10, entry 14-16).
To summarize, the best conditions for the bis-alkoxycarbonylation of 1-phenyl-1-butyne with the isolated yield of the carbonylated product is reported into the Scheme 58.



Scheme 58. Bis-alkoxycarbonylation of 1-phenyl-1-butyne7a.

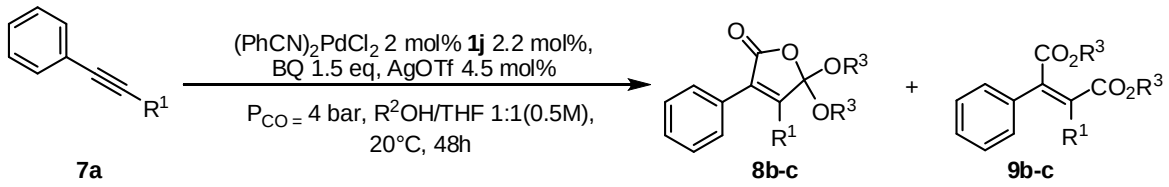
This methodology is the first example of bis-alcoxycarbonylation of internal alkynes that give dimethyl 2-ethyl-3-phenylmaleate **9a**. The poorly selectivity can be overcame by converting the cyclic derivatives **8a** into the dimethyl maleate **9a** with 80% yield, by means of Bronsted acid catalysis in methanol (Scheme 59).

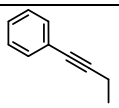
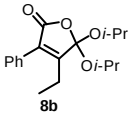
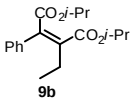
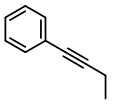
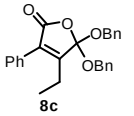
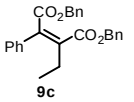


Scheme 59. Conversion of 8a into 9a.

We next start to investigate the generality of this new efficient catalytic system in the bis-alkoxycarbonylation. 1-phenyl-1-butyne **7a** in presence of different alcohols as nucleophiles, in place of methanol, is also tried in the bis-alkoxycarbonylation reaction. The preliminary result is reported into the Table 11.

Table 11. Bis-alcoxycarbonylation of 1-phenyl-1-butyne with different alcohols.



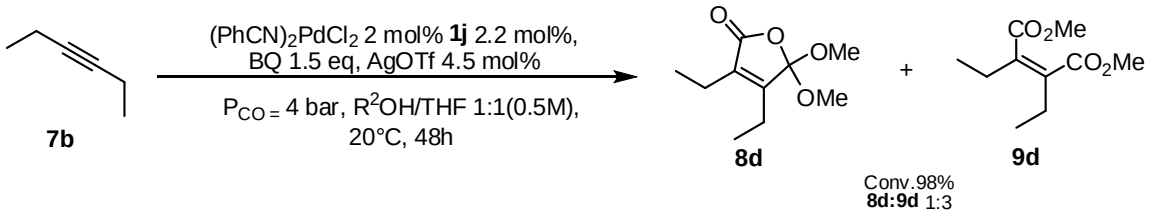
Entry [a]	Alkynes	R^2OH	Conv [b] %	8b-d [b]	9b-c [b]	**8b-c**: **9b-c** ratio [b]
1	 7a	*i*-prOH	60	 8b	 9b	1:1
2	 7a	BnOH	98	 8c	 9c	1:1

a) Reaction performed in autoclave at P_{CO}= 4 bar, with alkynes **7a, 8a** (2 mmol-scale), $(PhCN)_2PdCl_2$ 2 mol%, ligand **1j** 2,2 mol% (0.011 mmol), AgOTf 4.5 mol% and 1.5 eq of BQ (3 mmol) with THF/MeOH 1:1 (0.5 M) as reaction medium at 20°C, for 42 h.
b) Determined by direct ^{1}H NMR analysis of a sample of the reaction mixture.

Isopropyl alcohol, more hindered alcohol, is less active (Conv.= 60 %) than benzyl alcohol that was reactive enough to cause complete 1-phenyl-1-butyne conversion into the two bis-

carbonylated products **8c** and **9c**. In both case the ratio between the two products is the same and is equal to 1:1 and no beneficial effect of product selectivity is recorded.

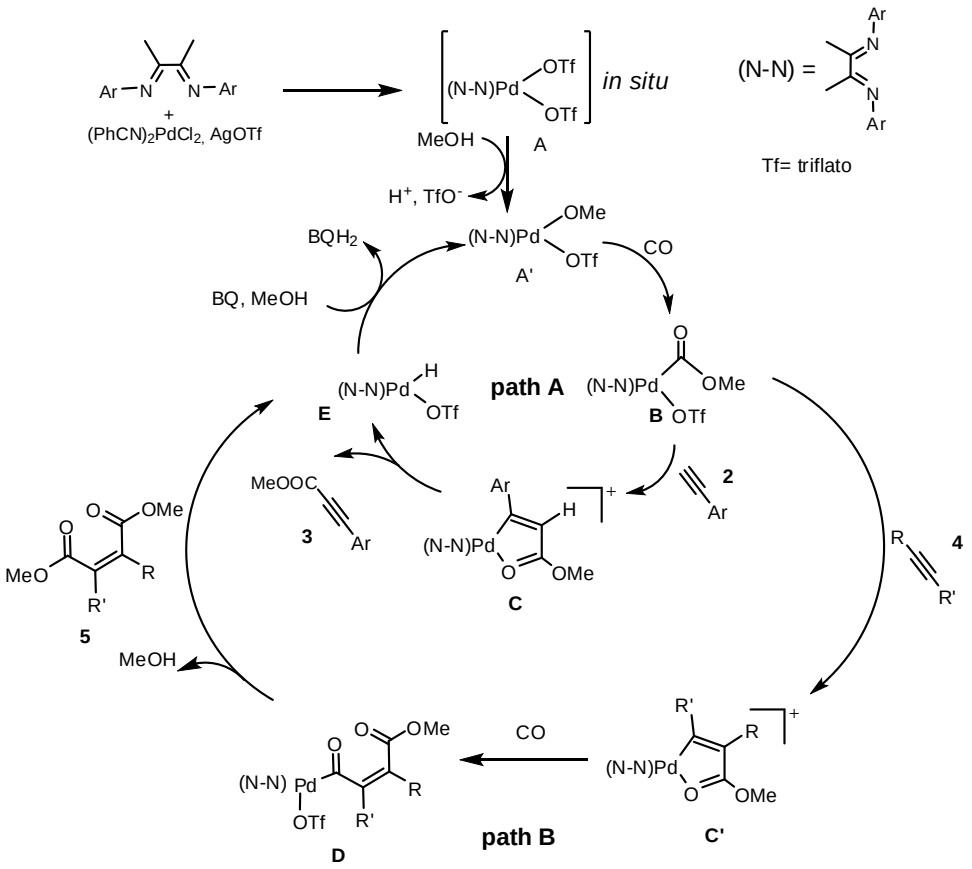
Reaction of bis-alcoxycarbonylation is tested also with hex-3-yne **7b** (Scheme 60), an aliphatic alkynes. Even with aliphatic alkyne **7b** the total conversion is achieved into the two bis-carbonylated products **8d**, **9d** and dimethyl 2,3-diethylmaleate **9d** in this case was the major product.



Scheme 60. Bis-alcoxycarbonylation of hex-3-yne

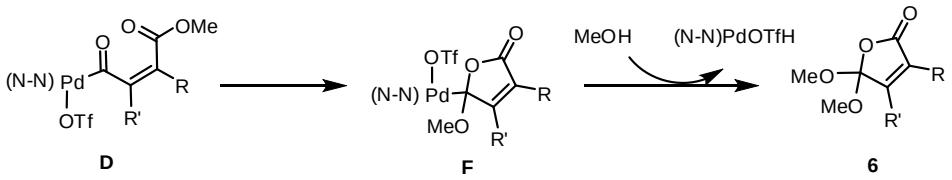
According to the literature data [101,108,112,122] and the result obtained, we can propose the reaction mechanism shown in the **path A** of Scheme 61 for the bis-alcoxycarbonylation of terminal alkenes and **path B** (Scheme 61) for the bis-alcoxycarbonylation of the internal alkynes. The first step of the reaction is the formation of the active species **A** (Scheme 61) from the reaction between $(PhCN)_2PdCl_2$ and DAB ligand in the presence of AgOTf. Active species **A** is converted into **A'** thanks to the replacement of OTf by OMe. Insertion of CO leads to the alkoxycarbonylpalladium complex **B**. After the insertion of the alkyne **2** (**path A,** Scheme 61**)** and alkyne **4** (**path B**, Scheme 61) the 5-membered palladacycle intermediate **C** and **C'** is formed. In the mechanism of the mono-alcoxycarbonylation of alkynes (Scheme 61, path a) the 5'-membered palladacycle intermediate **C** gives a β-hydride elimination to leads the final product **3** (Scheme 61) and the palladium hydride complex **E**.

While in the bis-alcoxycarbonylation of internal alkynes, hydrogen in β-position is not present and the β-hydride elimination does not occur. In this path, a second CO insertion in the 5-membered palladacycle intermediate **C'** gives complex **D** that undergo a nucleophilic displacement by the alcohol, leads to the final product **5** and the palladium hydride complex **E** (Scheme 61). Finally the presence of benzoquinone regenerates the active species **A** thus closing the catalytic cycle.[110]



Scheme 61. Proposed catalytic cycle.

In the bis-alcoxycarbonylation of internal alkynes the product **8a-d** is the result of intramolecular ring closing of the complex **D** following by nucleophilic attack of the methoxy (Scheme 62).[60]



Scheme 62. Intramolecular ring closing of the complex D.

In conclusion, we developed a new efficient and selectivity methodology for the mono-alkoxycarbonylation of terminal aromatic alkynes palladium catalyzed with S/C up to 1000:1. Moreover, for the first time, we reported the bis-alcoxycarbonylation of internal alkynes palladium catalyzed that produce derivatives of maleic diesters and them cyclic derivatives. The latter can be converted easily with highly yield in the acid condition into the maleic diesters.

7. Conclusions

To summary, the results presented in this section provide a new methodology for the palladium catalyzed oxidative carbonylation reactions of unsaturated molecules under milder reaction conditions.

Bis-alkoxycarbonylation reactions of aliphatic and aromatic olefins were successfully studied. By using the new aryl α-diimine ligand with extended aromatic rings, $Pd(TFA)_2$ and benzoquinone as the oxidant, esters of succinic acids were obtained with excellent yields and complete selectivity. Succinic acid derivatives represent valuable compounds useful in synthetic organic and medicinal chemistry. The optimized reaction conditions could be successfully applied on alkenes in the presence of different alcohols as nucleophiles, including the sterically hindered *i*-PrOH. Moreover, the oxidative carbonylation allowed a complete conversion of *cis* and *trans*-β-methylstyrene into two bis-carbonylated products with total diastereoselectivity.

On the other hand, the mono-alkoxycarbonylation reaction of variously substituted phenylacetylenes was selectively achieved by means of a sterically hindered Pd(II) complex bearing an aryl α-diimine as the ligand, formed *in situ* from $(PhCN)_2PdCl_2$ and AgOTf. For the first time, the same catalytic system was able to covert 1,2-substituted aliphatic and aromatic alkynes into a mixture of maleic acid esters and maleic acid cyclic derivatives.

8. Experimental Section

8.1 General Information

All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, in a stainless steel autoclave, by using Schlenk technique. Reactions were monitored by ^{1}H NMR taking a direct sample of the crude mixture. ^{1}H NMR and ^{13}C NMR were recorded on a Brucker Avance 200 spectrometer (^{1}H: 200 MHz, ^{13}C: 50 MHz) or Brucker Avance 400 spectrometer (^{1}H: 200 MHz, ^{13}C: 100 MHz) using $CDCl_3$ as solvent. Chemical shifts are reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and to the central line of $CDCl_3$ (77.10 ppm) for ^{13}C NMR. ^{13}C NMR were recorded with ^{1}H broadband decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd = double doublets, br = broad. Mass spectra were recorded on a LC-MS apparatus Waters 2795, Micromass ZQ using electrospray (ES+) ionisation techniques., Carbon monoxide (Cp grade 99.99%) was supplied by Air Liquide, benzoquinone was purchased by Sigma-Aldrich and was recrystallized from n-heptane/EtOH mixture, olefins **2a-o** were purchased from Sigma-Aldrich or Alfa Aesar, filtered off a plug of neutral Al_2O_3 and used without further purification. Alkynes **5a-d 5f-g** and **7a-b** were purchased from Sigma-Aldrich or Alfa Aesar, filtered off a plug of neutral Al_2O_3 and used without further purification. Alkynes **5e** was synthesized according with literature procedure.[126] Anhydrous THF was distilled from sodium-benzophenone, and methanol was distilled from $Mg(OMe)_2$. $Pd(TFA)_2$ and $PdCl_2(PhCN)_2$ was weighted in an analytical balance without excluding moist and air. AgOTf was dried with vacuum pump warming up to 120 °C for 30 minutes and was weighted in an analytical balance without excluding moist and air. Alcohols were degassed and stored over 4 Å molecular sieves. All other chemicals were purchased from Sigma-Aldrich and used without further purification. Ligands **1a, 1e, 1f, 1k, 1l, 1m**, used in the optimization reaction.[127] Ligand **1h, 1j** were synthesized according to previously reported procedure.[128] Ligand **1i** was synthesized by our group according to a previously reported procedure.[129]

8.2 Bis-alkoxicarbonylation of Alkenes

Synthesis of (*N*,*N'E*,*N*,*N'E*)-*N*,*N'*-(butane-2,3-diylidene)dianthracen-9-amine **1i**.

[126] Feng, Y.-S.; Xie, C.-Q.; Qiao, W.-L.; Xu, H.-J. *Org. Lett.*, *15*, 2013.
[127] tom Dieck, H.; Svoboda, M.; Grieser, T. *Z. Naturforsh* **1981**, *36b*, 832.
[128] van Asselt, R.; Elsevier, C. J.; Smeets, W. J. J.; Spek, A. L.; Benedix, R. *Recl. Trav. Pays-Bas* **1994**, *113*, 88298.
[129] Carfagna, C.; Gatti, G.; Paoli, P.; Binotti, B.; Fini, F.; Passeri, A.; Rossi, P.; Gabriele, B. *Organometallics* **2014**, *33*, 129.

9-Aminoanthracene **1** was synthesized as follows: palladium on charcoal (10%, 30 mg) was added to a solution of 9-nitroanthracene (300 mg, 1.34 mmol) in ethyl acetate (15 mL) with H_2 (atmospheric pressure), and stirred for 3 h at 20°C. The mixture was then filtered under nitrogen atmosphere and the solvent was evaporated under vacuum. 9-Aminoanthracene **1** was obtained as a yellow powder (242 mg, 1.25 mmol; yield 94%). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.98-7.90, 7.47-7.40 (m, 9H), 4.87 (brs, 2H; N*H*$_2$). Ligand **g** was synthesized as follows: 2,3-butanedione (85 μL, 0.97 mmol) and one drop of formic acid were added to a solution of (9-$C_{14}H_9$)NH_2 (374 mg, 1.94 mmol) in methanol (1 mL), and the mixture was stirred overnight at 25 °C. The formed precipitate was collected by filtration, washed with cold methanol and dried under vacuum. Ligand **g** was obtained as an orange powder (245 mg, 0.56 mmol; yield 58%).
^{1}H NMR (200 MHz, CD_2Cl_2): δ 8.32 (s, 2H), 8.10 (d, J= 5.1 Hz, 4H;), 7.91 (d, J = 4.3 Hz, 4H), 7.56 (m, 8H), 2.26 ppm (s, 6H); ^{13}C NMR (50 MHz, CD_2Cl_2): δ 170.8, 143.1, 131.84, 128.4, 125.6, 125.2, 123.5, 121.8, 119.7, 16.9.

8.2.1 Typical Procedure for the Bis-alkoxycarbonylation Reaction of Olefins.

In a nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the $Pd(TFA)_2$ (3.3 mg, 0.01 mmol) and THF (0.5 mL) were added in sequence. After the mixture turned in a red/brown color (20 min), the ligand **1i** (4.8 mg, 0.011 mmol) was added. The mixture was left stirring for 10 min, turning in a dark-green color. The formed catalyst was injected in a nitrogen flushed autoclave, equipped with a magnetic stirring bar, containing benzoquinone (325 mg, 3 mmol) and p-TSA·H_2O (7.6 mg, 0.04 mmol) in MeOH (3.5 mL). After 10 min of stirring, olefins 2a-o (2 mmol) were added in one portion in the reaction mixture. The autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at the room temperature (20°C) for 66 h. The autoclave was vented off, flushed with nitrogen and the reaction mixture was directly analyzed by ^{1}H NMR to determine the conversion and the ratio of the product 3 and 4. The crude was then dried under reduced pressure and filtered off a plug of silica gel, washing with CH_2Cl_2/Et_2O 8:2 (25 mL) finally the solution was dried up in vacuum. The product was eventually obtained after column chromatography on silica gel (Petroleum ether/CH_2Cl_2 50:50 then 30:70).

-Dimethyl 2-phenylsuccinate **3a**.
Following the general procedure, compound **3a** was obtained as a pale yellow wax in 91% of isolated yield.
^{1}H NMR (200 MHz, $CDCl_3$):δ 7.25 - 7.34 (m, 5 H), 4.09 - 4.13 (m, 1 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.17 - 3.26 (m, 1 H), 2.64 - 2.71 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.3, 171.9, 137.6, 128.8, 127.6, 127.5, 52.3, 51.8, 46.9, 37.5.

-Dimethyl 2-p-tolylsuccinate 3b.

Following the general procedure, compound **3b** was obtained as a pale yellow oil in 97% of isolated yield.
^{1} H NMR (200 MHz, $CDCl_3$): δ 7.12 - 7.19 (m, 4 H), 4.04 - 4.09 (m, 1 H), 3.67 (s, 6 H), 3.15 - 3.24 (m, 1 H), 2.62 - 2.68 (m, 1 H), 2.32 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ173.4, 171.8, 137.3, 134.5, 129.4, 127.4, 52.1, 51.6, 46.5, 37.4, 20.8.

-Dimethyl 2-(4-methoxyphenyl)succinate **3c**.
Following the general procedure, but performing the reaction with 2 mol % catalyst loading (13.3 mg, 0.04 mmol of $Pd(TFA)_2$ and 19.2 mg, 0.044 mmol of **1i**) using MeOH/THF 7:1 (0.25M) as the reaction medium, product **3c** was obtained in 88% of isolated yield (the presence of 7% of by-product **4c** was detected by using
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19 - 7.22 (m, 2 H), 6.85 - 6.89 (m, 2 H), 4.02 - 4.07 (m, 1 H), 3.81 (s, 3 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.13 - 3.23 (m, 1 H), 2.62 - 2.69 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.6, 171.9, 158.9, 129.6, 128.7, 114.1, 55.1, 52.2, 51.7, 46.1, 37.6.

-Dimethyl 2-(4-cyanophenyl)succinate **3d**.
Following the general procedure compound **3d** was obtained as a colorless oil in 90% of isolated yield (the presence of 7% of by-product **4d** was detected by using ^{1}H NMR analysis on a direct sample of the reaction mixture).
^{1} H NMR (200 MHz, $CDCl_3$): δ 7.62 (dd, JH-H = 7 Hz, 2 Hz, 2 H), 7.40 (d, JH-H = 8 Hz, 2 H), 4.15 (dd, JH-H = 9 Hz, 6 Hz, 1 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 3.18 (dd, JH-H = 17 Hz, 9= Hz, 1 H), 2.69 (dd, JH-H = 17 Hz, 6 Hz, 1 H); ^{13}C NMR (50 MHz, CDCl3): δ 172.2, 171.2, 142.8, 132.6, 128.7, 118.3, 111.8, 52.6, 51.9, 47.1, 37.1

-Dimethyl 2-(4-bromophenyl)succinate **3e**.
Following the general procedure, compound **3e** was obtained as a pale yellow wax in 96% of isolated yield.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 - 7.49 (m, 2 H), 7.16 - 7.20 (m, 2 H), 4.04 - 4.09 (m, 1 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.13 - 3.22 (m, 1 H), 2.62 - 2.70 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 171.5, 136.5, 131.9, 129.4, 121.6, 52.3, 51.8, 46.4, 37.2.

-Dimethyl 2-(4-chlorophenyl)succinate **3f**.
Following the general procedure, compound **3f** was obtained as a pale yellow oil in 91% of isolated yield.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 - 7.32 (m, 2 H), 7.22 - 7.25 (m, 2 H), 4.05 - 4.10 (m, 1 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 3.14 - 3.23 (m, 1 H), 2.63 - 2.70 (m, 1 H); 13C NMR (50 MHz, $CDCl_3$): δ 172.9, 171.6, 136.0, 133.6, 129.1, 128.9, 52.4, 51.9, 46.4, 37.3.

-Dimethyl 2-(2-chlorophenyl)succinate **3g**.

Following the general procedure, compound **3g** was obtained as a pale yellow oil; yield: 94% (over a conversion of 75% of 2-chlorostyrene 2g, determined by 1H NMR analysis on a direct sample of the reaction mixture).
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47–7.13 (m, 4H), 4.60 (dd, J=9.8, 5.1 Hz, 1 H), 3.67 (s, 3H), 3.66 (s, 3H), 3.13 (dd, J=17.0, 9.8 Hz, 1 H), 2.65 (dd, J=17.0, 5.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.9, 171.7, 135.6, 133.6, 130.0, 128.9, 128.8, 127.3, 52.4, 51.9, 44.0, 36.4; ESI-MS: m/z=257 [M+H]+.

-Dimethyl 2-(2-bromophenyl)succinate **3h**.
Following the general procedure, compound 3h was obtained as a pale yellow oil; yield: 91% (over a conversion of 45% of 2-bromostyrene 2h, determined by 1H NMR analysis on a direct sample of the reaction mixture).
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.61–7.54 (m, 1H), 7.30–7.21 (m, 2 H), 7.18–7.07 (m, 1 H), 4.63 (dd, J= 10.0, 4.9 Hz, 1 H), 3.66 (s, 3 H), 3.64 (s, 3 H), 3.12 (dd, J= 17.0, 10.0 Hz, 1H), 2.68 (dd, J=17.0, 5.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.9, 171.7, 137.4, 133.4, 129.1, 128.8, 128.0, 124.3, 52.5, 52.0, 46.4, 36.7; ESI-MS: m/z=301 [M+H]+.

-Dimethyl 2-(3-(trifluoromethyl)phenyl)succinate **3i**.
Following the general procedure, compound **3i** was obtained as a colorless oil in 85% of isolated yield.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59–7.40 (m, 4H), 4.15 (dd, *J* = 5.5 Hz, 9.8 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.21 (dd, *J* = 9.7, 17.0 Hz, 1H), 3.21 (dd, *J* = 5.5, 17.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 171.6, 138.7, 131,30 (q, *J* = 1.1 Hz), 131,28 (q, *J* = 32.4 Hz), 129.5, 124,74 (q, *J* = 3.7 Hz), 124,69 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.4 Hz), 52.6, 52.0, 46.9, 37.4. ESI-MS m/z 291 $[M+H]^+$.

-Dimethyl 2-(naphthalen-2-yl)succinate **3j**.
Following the general procedure, but introducing the vinyl naphthalene **2j** together with benzoquinone and p-TSA in the stainless steel autoclave and performing the reaction with 1 mol% catalyst loading (6.6 mg, 0.02 mmol of $Pd(TFA)_2$ and 9.6 mg, 0.022 mmol of **1i**), compound **3j** was obtained as a pale yellow wax in 87% of isolated yield (the presence of 7% of by-product **4j** was detected by using ^{1}H NMR analysis on a direct sample of the reaction mixture).
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 - 7.81 (m, 4 H), 7.38 - 7.47 (m, 3 H), 4.25 - 4.30 (m, 1 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.27 - 3.36 (m, 1 H), 2.72 - 2.79 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.3, 171.8, 134.9, 133.3, 132.7, 128.6, 127.7, 127.5, 126.6, 126.3, 126.0, 125.5, 52.3, 51.7, 47.1, 37.5;

-Dimethyl 2-pentylsuccinate **3k**.
Following the general procedure, but performing the reaction with 1 mol% catalyst loading, 6.6 mg, 0.02 mmol of $Pd(TFA)_2$ and 9.6 mg, 0.022 mmol of **1i** compound **3k** was obtained as a colorless oil; yield: 92%.

^{1}H NMR: (200 MHz, $CDCl_3$): δ 3.70 (s, 3 H), 3.68 (s, 3 H), 2.93–2.64 (m, 2 H), 2.44 (dd, J=15.9, 4.6 Hz, 1 H), 1.72–1.43 (m, 2H) 1.39–1.13 (m, 6 H), 0.97–0.79 (m, 3H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 175.7, 172.7, 51.8, 51.7, 41.1, 35.7, 31.8, 31.4, 26.5, 22.3, 13.9; ESI-MS: m/z=217 [M+H]+.

-Dimethyl 2-phenethylsuccinate **3l**.
Following the general procedure, but performing the reaction with 1 mol% catalyst loading, 6.6 mg, 0.02 mmol of $Pd(TFA)_2$ and 9.6 mg, 0.022 mmol of **1i**, compound **3l** was obtained as a pale yellow oil in 77% of isolated yield.
^{1} H NMR (200 MHz, $CDCl_3$): δ 7.29 - 7.26 (m, 2 H), 7.20 - 7.16 (m, 3 H), 3.70 (s, 3 H), 3.66 (s, 3 H), 2.92 – 2.86 (m, 1 H), 2.76 (dd, 1 H), 2.68 – 2.58 (m, 2 H), 2.48 (dd, 1 H), 2.03 – 1.95 (m, 1 H), 1.86 – 1.79 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 172.1, 141.0, 128.4, 128.3, 126.0, 51.8, 51.7, 40.7, 35.8, 33.5, 33.1.

-Dimethyl 2-tert-butylsuccinate **3m**.
Following the general procedure, but performing the reaction with 2 mol% of catalyst loading, 13.3 mg, 0.04 mmol of $Pd(TFA)_2$ and 19.2 mg, 0.044 mmol of **1i**, compound **3m** was obtained as a pale yellow oil; yield: 95% (over a conversion of 53% of 3,3-methyl-1-butene 2m).
^{1}H NMR (200 MHz, $CDCl_3$): δ 3.66 (s, 3 H), 3.63 (s, 3H), 2.85–2.39 (m, 3 H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 173.3, 51.9, 51.4, 51.3, 32.7, 27.9; ESI-MS: m/z=203 [M+H]+.

-Diisopropyl 2-phenylsuccinate **3n**.
Following the general procedure, but performing the reaction with 2 mol% catalyst loading, 13.3 mg, 0.04 mmol of $Pd(TFA)_2$ and 19.2 mg, 0.044 mmol of **1i** and using i-PrOH as the alcohol, compound **3n** was obtained as a colorless oil; yield: 92%.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26 (br s, 5H), 4.98 (hept, J=6.3 Hz, 1 H), 4.97 (hept, J=6.2 Hz, 1 H), 4.01 (dd, J=5.5, 10.2 Hz, 1 H), 3.12 (dd, J=10.2, 16.7 Hz, 1 H), 2.60 (dd, J=5.5, 16.7 Hz, 1H), 1.22 (d, J=6.3 Hz, 3 H), 1.19 (d, J=6.2 Hz, 3 H), 1.16 (d, J=6.2 Hz, 3 H), 1.08 (d, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 171.0, 138.0, 128.7, 127.7, 127.4, 68.4, 68.1, 47.5, 38.2, 21.7, 21.7, 21.4; ESI-MS: m/z=278 [M+H]+.

-Dibenzyl 2-phenylsuccinate **3o**.
Following the general procedure, but performing the reaction with 2 mol% catalyst loading, 13.3 mg, 0.04 mmol of $Pd(TFA)_2$ and 19.2 mg, 0.044 mmol of **1i**, and using BnOH as the alcohol, compound **3o** was obtained as a colorless oil; yield: 94%.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.51–7.09 (m, 15H), 5.10 (br s, 4 H), 4.18 (dd, J=9.9, 5.5 Hz, 1 H), 3.29 (dd, J=16.9, 10.0 Hz, 1 H), 2.77 (dd, J=16.9, 5.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 171.3, 137.5, 135.8, 135.7, 128.9, 128.6, 128.50, 128.33, 128.28, 128.2, 127.9, 127.8, 66.8, 66.7, 47.4, 37.8; ESI-MS: m/z=375 [M+H]+.

-(2R*,3R*)-Dimethyl 2-methyl-3-phenylsuccinate **3p**.
Following the general procedure, but performing the reaction with 2 mol% of catalyst loading, 13.3 mg, 0.04 mmol of $Pd(TFA)_2$ and 19.2 mg, 0.044 mmol of **1i**, compound **3p** was obtained as a pale yellow wax; yield: 92%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.21 (m, 5 H), 3.81 (d, J=10.9 Hz, 1H), 3.65 (s, 3 H), 3.40 (s, 3 H), 3.24 (dq, J=10.9, 6.8 Hz, 1 H), 1.28 (d, J= 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.3, 172.5, 136.6, 128.4, 128.1, 127.6, 54.6, 51.9, 51.3, 43.6, 16.2; ESI-MS: m/z=237 [M+H]+.

-(2S*,3R*)-Dimethyl 2-methyl-3-phenylsuccinate **3q**.
Following the general procedure, but performing the reaction with 2 mol% of catalyst loading, 13.3 mg, 0.04 mmol of $Pd(TFA)_2$ and 19.2 mg, 0.044 mmol of **1i**, compound **3q** was obtained as a pale yellow oil; yield: 87%. ^{1}H NMR (200 MHz, $CDCl_3$): 7.44–7.25 (m, 5 H), 3.81 (d, J=11.4 Hz, 1H), 3.77 (s, 3 H), 3.67 (s, 3 H), 3.21 (dq, J=11.3, 7.3 Hz, 1 H), 0.99 (d, J= 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.0, 173.6, 136.2, 128.8, 128.3,127.7, 54.1, 52.0, 51.9, 42.2, 15.3; ESI-MS: m/z=237 [M+H]+.

8.3 Oxidative Alkoxycarbonylation of Alkynes

8.3.1 Typical Procedure for the Mono-alkoxycarbonylation Reaction of Terminal Alkynes

In a nitrogen flushed Schlenk tube equipped with a magnetic stirring bar were added in sequence the $PdCl_2(PhCN)_2$ (3.8 mg, 0.01 mmol) and THF (2 mL), after the mixture turned in a red/brown color (20 min). The ligand **1j** (5.0 mg, 0.011 mmol) was added, the mixture was left stirring for 10 min and turning in an dark orange color. AgOTf (23.2 mg, 0.09 mmol) was added in one portion, the mixture turned in a light orange color with development of yellowish solid. The preformed catalyst was injected in a nitrogen flushed autoclave containing benzoquinone (325 mg, 3 mmol) in ROH (2 mL). After 10 min the olefin **5a-g** (2 mmol) were added in one portion in the reaction mixture by using a syringe. The autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at the room temperature (20°C) for 44 h. The autoclave was vented off, flushed with nitrogen and the reaction mixture was directly analyzed by ^{1}H NMR to determine the conversion and the ratio of the products **8a-d:9a-d**. The crude was then dried under reduced pressure and filtered off a plug of silica gel, washing with CH_2Cl_2 (100 ml) finally the solution was dried up in vacuum. Products were eventually obtained after column chromatography on silica gel (Petroleum ether/CH_2Cl_2 70:30 then 50:50).

-Methyl 3-phenylpropiolate **6a**.
Following the general procedure, compound **6a** was obtained as a pale yellow oil in 90% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64-7.55 (m, 2H), 7.52-7.30 (m, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 154.6,133.1, 130.8, 128.7, 119.6, 86.6, 80.4, 52.9.

-Methyl 3-(4-methoxyphenyl)propiolate **6b**

Following the general procedure, compound **6b** was obtained as a pale yellow wax in 82% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57-7.49 (m, 2H), 6.92-6.84 (m, 2H), 3.83 (s, 3H), 3.82(s,3H).^{13}C-NMR(100 MHz, CDCl3) δ 161.7, 154.8, 135.0, 114.4, 111.4, 87.5, 56.5, 52.8.

-Methyl 3-(2-(trifluoromethyl)phenyl)propiolate **6c**.

Following the general procedure, compound **6c** was obtained as a pale orange-yellow wax in 53% yield.

^{1}H NMR (400 MHz, $CDCl_3$) 7.76-7.68 (m, 2 H), 7.58-7.54 (m, 2H), 3.85 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 135.4, 133.0 (q, J $^{(C-F)}$ = 31.3 Hz), 131.8, 130.5, 126.3 (q, J $^{(C-F)}$ = 5 Hz),128.5, 119.7, 84.9, 81.60, 53.1.

-Methyl 3-(4-fluorophenyl)propiolate **6d**.

Following the general procedure, compound **6d** was obtained as a white wax in 71% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64-7.53 (m, 2H), 7.07 (t, J= 8.7 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.1(d, $J^{(C-F)}$ = 245 Hz), 154.5, 135.42 (d, $J^{(C-F)}$ = 8.9 Hz), 116.29 (d, $J^{(C-F)}$ = 22.4 Hz), 115.8 (d, $J^{(C-F)}$ = 3.6 Hz), 85.6, 80.4 (d, $J^{(C-F)}$ = 1.5 Hz), 53.0.

-1-ethynyl-4-nitrobenzene **5e**.

The mixture of 1-iodo-4-nitrobenzene (500 mg, 1 mmol), $Pd(PPh_3)_2C1_2$ (5 mol %, 86.6mg) and CuI (5 mol%, 23mg) in Et_3N (30 mL) was added dropwise via cannula a solution of (trimethylsilyl)acetylene (1.1 equiv, 1.93 mg) in Et_3N (10 mL) at rt for 6 h (Monitored by TLC), and a purification by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 50:1) to give trimethyl((4-nitrophenyl)ethynyl)silane (276 mg, 1.3 mmol, 51% yield). To a solution of trimethyl((4-nitrophenyl)ethynyl)silane (276 mg 1.26 mmol) in 26 mL of diehy1 ether/methanol (1:1) and 5 mL of a 10% sodium hydroxide solution at rt for 35 min (Monitored by TLC). The reaction mixture was neutralized with a 1 M HCl solution. Chromatography on silica gel (eluent: petroleum ether/ethyl acetate 50:1) afforded the product 1h as yellow solid. Yield: 147 mg (84%).This compound is known.

^{1}H NMR (200 MHz, CDCl3) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 3.35 (s, 1H).

^{13}C NMR (50 MHz, CDCl3) δ147.48, 132.98, 128.92, 123.59, 82.35, 81.58.

-Methyl 3-(4-nitrophenyl)propiolate **6e**.

Following the general procedure, on 1 mol of substrate the reaction was carried out with 2 mol% of catalyst loading, 13.3 mg, 0.02 mmol of $PdCl_2(PhCN)_2$ and 7.7 mg, 0.022 mmol of **1j**, 0.044 of AgOTf, compound **6e** was obtained as a pale yellow solid in 31% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J=9.0 Hz, 2H), 7.74 (d, J= 9.0 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.7, 133.8, 126.3,123.9, 84.0, 53.3.

-Isopropyl 3-phenylpropiolate **6f**.
Following the general procedure, compound **6f** was obtained as a pale yellow oil in 92% yield.
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62-7.54 (m, 2H), 7.49-7.31 (m, 3H), 5.12 (hept, J= 6.3 Hz, 1H), 1.34 (d, J= 6.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.8, 130.1, 130.6, 128.7, 119.9, 85.8, 81.2, 70.1, 21.8.

-*Tert*-butyl 3-phenylpropiolate **6g**.
Following the general procedure, compound **6g** was obtained as a pale yellow oil in 73% yield.
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61-7.53 (m, 2H), 7.48-7.30 (m, 3H), 1.54 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.3, 133.0, 130.4, 128.6, 120.1, 83.9, 83.6, 82.1, 28.2.

-Benzyl 3-phenylpropiolate **6h**.
Following the general procedure, compound **6h** was obtained as a colorless oil in 75% yield. .
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63-7.54 (m, 2H), 7.42-7.31 (m, 3H), 5.27 (s, 9H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.89, 134.90, 133.00, 130.67, 128.65, 128.61, 128.55, 119.53, 86.71, 80.47, 77.20, 67.69.

-Cyclopentyl 3-phenylpropiolate **6i**.
Following the general procedure, the reaction with 1 mol% of catalyst loading, 13.3 mg, 0.02 mmol of $PdCl_2(PhCN)_2$ and 7.7 mg, 0.022 mmol of **1j**, 0.044 of AgOTf, compound **6i** was obtained as a pale yellow solid in 75% yield.
^{1}H NMR (400 MHz, $CDCl_3$)7.61-7.56 (m, 2H), 7.47-7.41 (m, 1H), 7.40-7.33 (m, 2H), 5.34-5.28 (m, 1H), 1.98-1.60 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 133.1, 130.6, 128.6, 119.9, 85.8, 81.2, 79.4, 32.7, 23.8.

-*Sec*-butyl 3-phenylpropiolate **6j**.
Following the general procedure, compound **6j** was obtained as a pale yellow solid in 60% yield.
^{1}H NMR (400 MHz, $CDCl_3$) 7.63 -7.54 (m, 2H), 7.47-7.41 (m, 1H), 5.05-4.96 (m, 2H), 1.77-1.59 (m, 2H), 1.31 (d, 3H), 0.96 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 132.9, 130.6, 128.6, 119.7, 85.7, 81.1, 74.6, 28.7, 19.4, 9.7.

-1-phenylethyl 3-phenylpropiolate **6k**.
Following the general procedure, compound **6k** was obtained as a pale yellow solid in 56% yield.
^{1}H NMR (400 MHz, $CDCl_3$) 7.62 -7.56 (m, 2H), 7.49-7.30 (m, 8H), 6.04 (q, J= 6.6 Hz, 1H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 140.7, 133.0, 130.7,, 128.9, 128.6, 128.3, 126.4, 119.7, 86.3, 80.9, 74.6, 74.4, 22.1

-Methyl hept-2-ynoate **6m**.
Following the general procedure, compound **6m** was obtained as a colorless oil in 10% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.62-1.47 (m, 2H), 1.49-1.36 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 140.7, 90.0, 73.0, 52.7, 29.6, 22.0, 18.5, 13.6.

-(E)-methyl 3-methoxyhept-2-enoate **6m'**.
Following the general procedure, compound **6m'** was obtained as a colorless oil in 10% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.99 (s, 1H), 3.80 – 3.73 (m, 1H), 3.66 (d, *J* = 7.6 Hz, 3H), 2.82 – 2.61 (m, 2H), 1.73 – 1.00 (m, 10H), 1.00 – 0.72 (m, 12H).

-Methyl 3-mesitylpropiolate **6l**.
Following the general procedure compound **6l** was obtained as an orange yellow wax in 14% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.89 (s, 2H), 3.84 (s, 3H), 2.44 (s, 6H), 2.29 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.0, 142.6, 140.7, 128.0, 116.5, 88.0, 85.1, 52.8, 21.6, 20.9.

-1-mesitylethanone **6l'**.
Following the general procedure compound **6l'** was obtained as an orange yellow wax in 30% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.86 (s, 2H), 2.48 (s, 3H), 2.28 (s, 3H), 2.24 (s, 6H). ^{13}C NMR (50 MHz, CDCl3) δ 208.62, 139.89, 138.31, 132.31, 128.50, 32.23, 21.02, 19.11.

8.3.2 Typical Procedure for the Bis-alkoxycarbonylation reaction of Internal Alkynes

In a nitrogen flushed Schlenk tube equipped with a magnetic stirring bar were added in sequence the $PdCl_2(PhCN)_2$ (15.3 mg, 0.04 mmol) and THF (2 mL), after the mixture turned in a red/brown color (20 min). The ligand **1j** (22.0 mg, 0.044 mmol) was added, the mixture was left stirring for 10 min and turning in an dark orange color. AgOTf (23.2 mg, 0.09 mmol) was added in one portion, the mixture turned in a light orange color with development of yellowish solid. The preformed catalyst was injected in a nitrogen flushed autoclave containing benzoquinone (325 mg, 3 mmol) in ROH (2 mL). After 10 min the olefin **7a-b** (2 mmol) were added in one portion in the reaction mixture by using a syringe. The autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at the room temperature (20°C) for 44 h. The autoclave was vented off, flushed with nitrogen and the reaction mixture was directly analyzed by ^{1}H NMR to determine the conversion and the ratio of the product **8a-d:9a-d**. The crude was then dried under reduced pressure and filtered off a plug of silica gel, washing with CH_2Cl_2 (100 ml) finally the solution was dried up in vacuum. The product for the characterization was eventually obtained after column chromatography on silica gel (Petroleum ether/CH_2Cl_2 50:50 to 20:80).

-4-ethyl-5,5-dimethoxy-3-phenylfuran-2(5H)-one **8a**.

Following the general procedure, compound **8a** was obtained as a pale yellow wax e in 48% yield.
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69-7.60 (m, 2H), 7.49-7.40 (m, 3H), 3.43 (s, 6H), 2.68-2.44 (m, 2H), 1.23 (t, 3H),. ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.5, 150.0, 133.4, 130.3, 129.8, 128.9, 128.6, 120.0, 51.76, 18.0, 12.7. ESI-MS: m/z=249 [M+H]+.

-Dimethyl 2-ethyl-3-phenylmaleate **9a.**
Following the general procedure, compound **9a** was obtained as a colorless oil in 41% yield.
^{1}H NMR (200 MHz) δ 7.46-7.32 (m 3H), 7.32-7.22 (m, 2H), 3.85 (s, 3H), 3.73 (s, 3H), 2.25 (q, J= 7.5Hz, 2H), 1.02 (t, J= 7.5Hz, 3H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.0, 168.2, 141.6, 137.5, 134.7, 128.7, 128.6, 128.5, 52.60, 52.44, 24.04, 12.93. ESI-MS: m/z=249 [M+H]+.

-4-ethyl-5,5-diisopropoxy-3-phenylfuran-2(5H)-one **8b**.
Following the general procedure, compound **5d** was obtained as a pale yellow wax. **^{1}H NMR** (200 MHz) *δ* ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 – 7.64 (m, 1H), 7.56 – 7.30 (m, 4H), 4.32 – 3.93 (m, 2H), 2.59 (m, 2H), 1.35 – 1.10 (m, 9H), 1.07 – 0.94 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.06, 158.91, 150.93, 132.24, 130.33, 129.90, 128.99, 128.82, 128.49, 120.24, 68.42, 68.05, 24.00, 23.93, 23.53, 23.32, 19.60, 12.49.

-Diisopropyl 2-ethyl-3-phenylmaleate **9b**.
Following the general procedure, compound **6d** was obtained as a colourless oil.
^{1}H NMR (200 MHz) δ 7.43-7.20 (m 5H), 5.30-4.95 (dm, 2H), 2.24 (q, J= 7.5 Hz, 2H), 1.32 (d, J= 6.2 Hz, 6H), 1.20 (d, J= 6.2Hz, 6H), 1.01 (t, J= 7.5Hz, 3H). ^{13}C NMR δ 167.9, 167.5, 140.4, 138.3, 135.3, 128.7, 128.4, 128.2, 68.9, 68.8, 24.0, 21.9, 21.7, 13.02.

-5,5-bis(benzyloxy)-4-ethyl-3-phenylfuran-2(5H)-one **8c**.
Following the general procedure, compound **5e** was obtained as a yellow wax.
^{1}H NMR (200 MHz) δ ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 – 7.08 (m,15H), 5.04 – 4.53 (m, 4H), 2.75 – 2.49 (q, 2H), 1.43 – 1.19 (t, 3H). ESI-MS: m/z=401 [M+H]+.

-Dibenzyl 2-ethyl-3-phenylmaleate **9c**.
Following the general procedure, compound **9c** was obtained as a yellow wax.
^{1}H NMR (200 MHz) δ 7.42-7.17 (m, 15H), 5.15 (s, 2H), 5.05 (s, 2H), 2.29 (q, J= 7.5Hz, 2H), 1.01 (t, J= 7.5Hz, 3H). ^{13}C NMR δ 168.2, 167.5, 141.0, 137.9, 135.6, 135.6, 134.8, 128.7, 128.6, 128.5, 128,48, 128.2, 128.2, 67.3, 67.1, 24.1, 13.0. ESI-MS: m/z=401 [M+H]+.

-3,4-diethyl-5,5-dimethoxyfuran-2(5H)-one **8d**.
Following the general procedure, compound **8d** was obtained as a colourless oil.
^{1}H NMR (200 MHz) δ 3.37 (s 6H), 2.32 (dq, J= 7.5 Hz, 4H), 1.17 (m, 6H) ^{13}C NMR δ 169.8, 156.0, 141.6, 133.3, 120.0, 51.6, 18.6, 17.0, 13.3, 12.0.

-Dimethyl 2,3-diethylmaleate **9d**.

Following the general procedure, compound **6c** was obtained as a colourless oil.
^{1}H NMR (200 MHz) δ 3.75 (s, 6H), 2.36 (q, J= 7.5 Hz, 4H), 2.25 (q, J= 7.5Hz, 2H), 1.05 (t, J= 7.5Hz, 6H) ^{13}C NMR δ 169.3, 138.8, 141.6, 52.2, 22.8, 12.9.

Section 2

Towards the Development of a New Strategy of the Synthesis of ^{18}F-FAC

9.1 Introduction

The term "Molecular Imaging" defines a group of techniques that permit the visualization of in vivo biological processes at molecular or cellular level using a specific imaging probe. One of the most sensitive molecular imaging technique is the positron emission tomography (PET).[130] This technique is based on the administration of radiolabeled molecule which decay by the emitting of a positively charged particle, the positron. The emitted positron travels a short distance in surrounding matter or tissue before annihilation with an electron, producing two simultaneous γ-rays (511 keV) in opposite directions (Figure 9). This process enables the location of the annihilation event and software reconstructs an image with information about the spatial distribution of radioactivity as a function of time.[131]

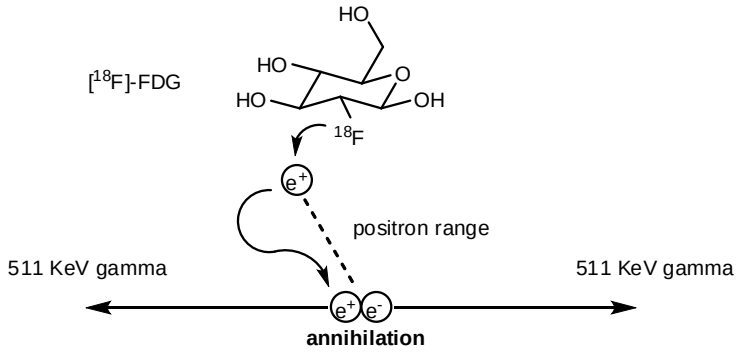


Figure 9. Principle of PET imaging. ^{18}F atom on the sugar molecule decays by emitting a positron.

PET is a useful technique for understanding biochemical processes both in humans and animal models. Furthermore PET technology enables further development of the "personalized medicine" approaches. It is able to elucidate the drug action and establish a dosage regimen of the central nervous system drug. Nuclei, typically used in PET, are for example ^{15}O, ^{13}N, ^{11}C and ^{18}F (Table 12).

Table 12. Physical properties of commonly used positron-emitting radionuclides.

Nuclide	Half time (min)	Maxium energy (MeV)	Mode of decay (%)	Theorical specific activity (GBq/μmol)
^{18}F	110	0.64	β+ (97%) EC[a] (3%)	6.3 x 10^4
^{11}C	20.3	0.97	β+ (99%)	3.4 x 10^5
^{13}N	10	1.20	β+ (100%)	7.0 x 10^5
^{15}O	2	1.74	β+ (100%)	3.4 x 10^6
^{76}Br	972	4.0	β+ (57%) EC (43%)	7.2 x 10^3
^{124}I	60192	2.14	β+ (25%) EC (75%)	1.15 x 10^3

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^{68}Ga	68.1	1.90	β+ (89%) EC (11%)	1.02 x 10^5

a) EC: electron capture

Fluorine receives considerable interest in medicinal chemistry, as it often exhibits useful physical proprieties for drug development, such as small Van Der Waals radius (1.47 Å), high electronegativity and higher bond energy with carbon in comparison to carbon hydrogen bond (C–F= 112 kcal/mol > C–H= 98 kcal/mol), and hence higher metabolic stability. In addition, fluorine-18 has a short half life (110 min), high positron decay ratio (97%) and low positron energy (max 0.64 MeV), which are all favorable parameters for PET. Based on these findings, a strong interest in ^{18}F radiolabeling of biologically relevant small molecules has arisen over the last decade. Prominent representative examples of fluorine-18 labeled PET imaging probes synthesized by nonisotopic substitution are 6-[^{18}F]-fluoro-3,4-dihydroxyphenylalanine ([^{18}F]6-fluoro-L-DOPA) (Figure 10, right), a PET ligand for probing cerebral dopamine metabolism [132] and neuroendocrine timors in humans.[133] While 2-[^{18}F]-fluoro-deoxy-D-glucose ([^{18}F]-FDG) (Figure 10, left), a glucose analog, is the best clinically known and the most successful commercial PET radiopharmaceutical. It is also a probe molecule for studying glucose metabolism.[134]

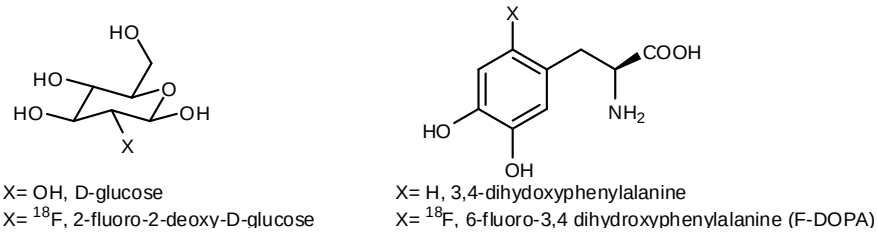

Figure 10. Structure of glucose, 3,4-dihydroxyphenylalanine and their respective fluoro-18 analogues.

The short half-life of fluorine-18 requires the development of synthetic pathways in which the radionuclide is introduced in a late stage step to counteract of the decay of the ^{18}F nucleus before injection into the body (Figure 11). Ideally, the synthesis the purification period should not exceed 2 to 3 times the physical half-time of the radionuclide in use. Practical reaction time goes from 1 to 30 min on the base of the physical half-time of the radioisotope in use. Reaction volume is typically 0.2-1 ml and reaction temperature can vary from room temperature to 190°C. Beside conventional heating, microware heating has a positive effect compared to conventional heating, in term of product selectivity, cleaning and velocity of the reaction.[135] Regarding the purification, highly level radiochemical purity (> 95%) is required

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[133] Becherer, A.; Szabó, M.; Karanikas, G.; Wunderbaldinger, P.; Angelberger, P.; Raderer, M.; Kurtaran, A.; Dudczak, R.; Kletter, K. *J. Nucl. Med.* **2004**, *45*, 1161.
[134] Reivick, M.; Kuhl, D.; Wolf, A.; Greenberg, J.; Phelps, M.; Ido, T.; Casella, V.; Hoffmann, E.; Alavi, A.; Sokoloff, L. *Circ. Res.* **1979**, *44*, 127.
[135] Lasne, M. C.; Perrio, C.; Rouden, J.; Barré, L.; Roeda, D.; Dollé, F.; Crouzel, C. *Top. Curr. Chem.* **2002**, *222*, 203.

for all PET radiopharmaceuticals for human and animal use. High pressure liquid chromatography (HPLC) purification guarantees a high level of purity also with the use of disposable cartridges.

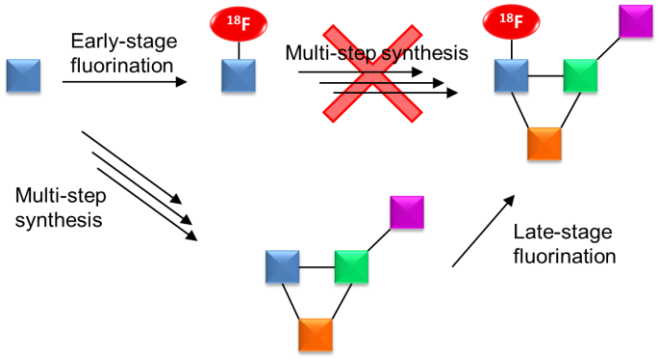
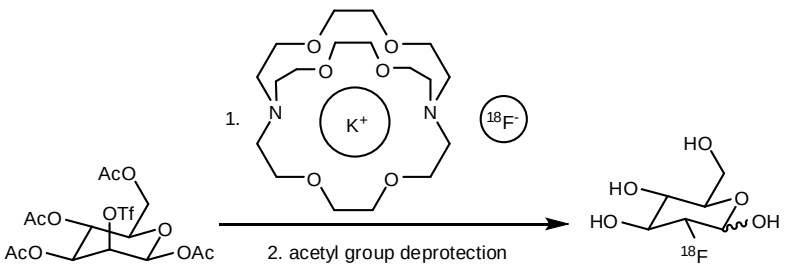


Figure 11. Schematic representation of the two different approaches for the synthesis of ^{18}F labeled complex molecules: the early-stage fluorination *Vs* late-stage fluorination.

Although a number of labeling reactions have been reported,[136] more complex molecules often still cannot be synthesized with ^{18}F. The variety of the reactions for the introduction of ^{18}F can be divided into two subgroups: nucleophilic and electrophilic fluorination.

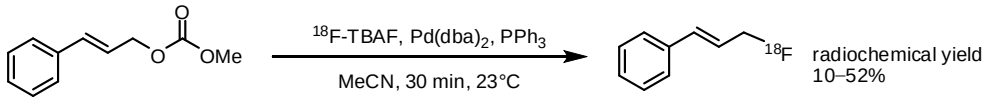
The nucleophilic ^{18}F-fluoride is produced by irradiation of oxygen-18 enriched water according to the ^{18}O (p,n) ^{18}F reaction. In the water a ^{18}F-fluorine is a poorly nucleophile and it is activated by applying cryptands in combination with alkali salts or tetra-n-butylammonium cation. The most commonly used cryptand in combination with potassium carbonate is the aminopolyether Kryptofix 2.2.2. complex and in this way the azacryptand K_{222} forms a strong complex with the potassium cation and leaves the fluoride ion exposed in dipolar aprotic solvent.[137] For aliphatic systems, the reaction goes through a S_N2 mechanism, from precursors bearing bromo, iodo, tosylate, nosylate and sulfonate as leaving group, with acetonitrile as reaction medium. While ^{18}F nucleophilic substitutions on the aromatic substrates occurs when the aromatic ring is activated by electron withdrawing substituents such as CN, CHO, NO_2, COOR and RCO in *ortho* and *para* position. Leaving groups are typically nitro and trimethylammonium salts.[138] Indeed, the most commonly used radiotracer for imaging, 2-deoxy-2-[^{18}F]fluoro-d-glucose (^{18}F-FDG), is made by nucleophilic substitution of a triflate leaving group on a mannose triflate derivative with ^{18}F-fluoride (Scheme 63).[139]

[136] Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M., S.; Scott, P. J.H. *Chem. Sci.* **2014**, *5*,4545-4553.
[137] a) Coenen, H. H.; Klatte, B.; Knöchel, A.; Schüller, M.; Stöcklin, G. J. *Labelled Compd. Radiopharm.* **1986**, *23*, 455. b) Hamacher, K.; Coenen, H. H.; Stöcklin, G. J. *Nucl. Med.* **1986**, *27*, 235.
[138] a) Coenen, H. H. *Synthesis and Application of Isotopically Labeled Compounds*; Elsevier: Amsterdam, 1989; p 433(40). Angeli, G.; Speranza, M.; Wolf, A. P.; Shiue, C. Y.; Fowler, J. S.;Watanabe, M. *J. Labelled Compd. Radiopharm.* **1984**, *21*, 1223.
[139] Hamacher, K.; Coenen, H. H.; Stocklin, G. *J. Nucl. Med.* **1986**, *27*, 235 – 238.



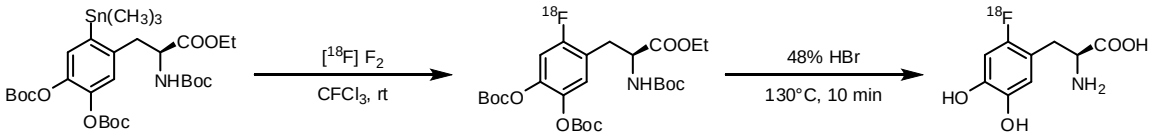
Scheme 63. Nucleophilic radiochemical fluorination with ^{18}F-fluoride.

While the first palladium-catalyzed fluorination reaction with ^{18}F-fluoride for the synthesis of ^{18}F-functionalized allylic fluorides is reported by Gouverneur and co-workers (Scheme 64).[140]



Scheme 64. Allylic fluorination with ^{18}F-fluoride catalyzed by Pd.

For electrophilic reactions, elemental ^{18}F-labeled fluorine ($^{18}F_2$) and its secondary derived precursors are used. The original method for the production of $^{18}F_2$ proceeds via bombardment of the target neon gas and with deuterons. A more recent approach uses a $^{18}O_2$ as target material in ^{18}O (p,n) ^{18}F reaction. [141] $^{18}F_2$ is high reactive and is generally converted into less reactive and more selective ^{18}F-labeled fluorination agent as acetyl hypofluorite,[142] xenon difluoride,[143] N-fluorosulfonamide[144] and ^{18}F-TEDA salts.[145] $^{18}F_2$ has found a wide application in the radiosynthesis of ^{18}F-DOPA although it can lead to multiple fluorinated products and are not functional-group tolerant (Scheme 65).[146]

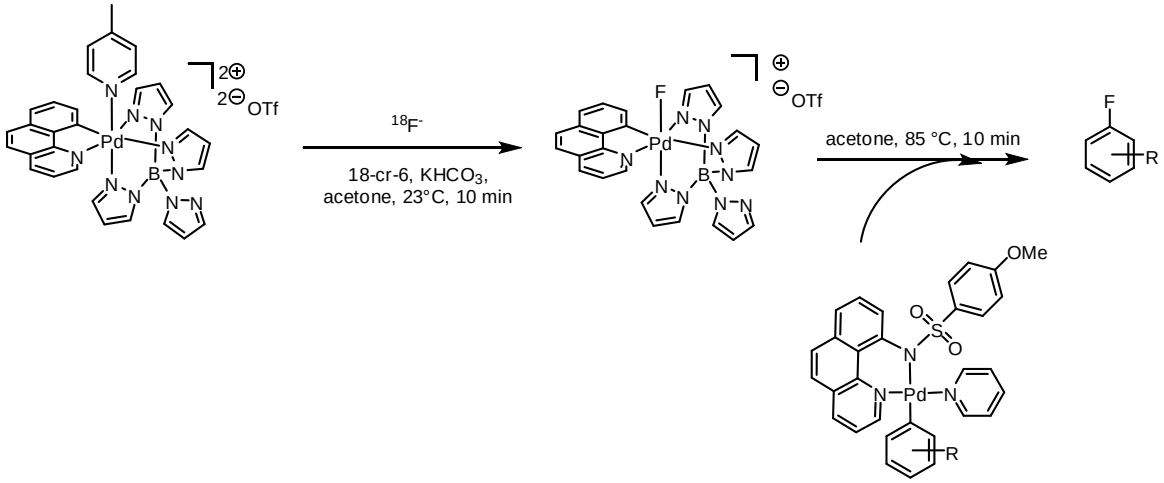


Scheme 65. Electrophilic radiosynthesis of ^{18}F-DOPA.

An electrophilic radiofluorination for the synthesis of aryl fluorides at a late stage. with high specific activity is achieved by using of Pd (IV) complex to incorporate ^{18}F-fluoride into

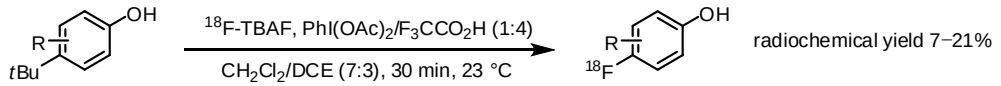
[140] Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 2613.
[141] Bishop, A.; Satyamurthy, N.; Bida, G.; Hendry, G.; Phelps, M.; Barrio, J. R. *Nucl. Med. Biol.* **1996**, *23*, 189.
[142] Fowler, J. S.; Shiue, C. Y.; Wolf, A. P.; Salvador, A. P.; MacGregor, R. R. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 1634.
[143] Chirakal, R.; Firnau, G.; Schrobigen, G. J.; MacKay, J.; Garnett, E. S. *Appl. Radiat. Isot.* **1984**, *35*, 401.
[144] Oberdorfer, F.; Hofmann, E.; Maier-Borst, W. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 999.
[145] Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 6821 –6824.
[146] a) Fimau, G.; Chirakal, R.; Garnett, E. S. *J. Nuc. Med.* **1984**, *25*: 1228. b) Namavari, M.; Bishop, A.; Satyamurthy, N.; Bida, G.; Barrio, J. R. *Int. J. Rad. Appl. Instrum. A.* **1992** *43*, 989. c) de Vries, E. F. J.; Luurtsema, G.; Brüssermann, M.; Elsinga, P. H.; Vaalburg, W. *Appl. Radiat. Isot.* **1999**, *51*, 389.

complex arenes.[147] The Pd (IV) complex captures fluoride and then functions as an electrophilic ^{18}F-fluorinating reagent (Scheme 66). Additionally, the Pd (IV)-^{18}F complex is thermally stable and insensitive to water.



Scheme 66. Synthesis of an electrophilic ^{18}F-Pd(IV) fluorinating reagent for the electrophilic fluorination.

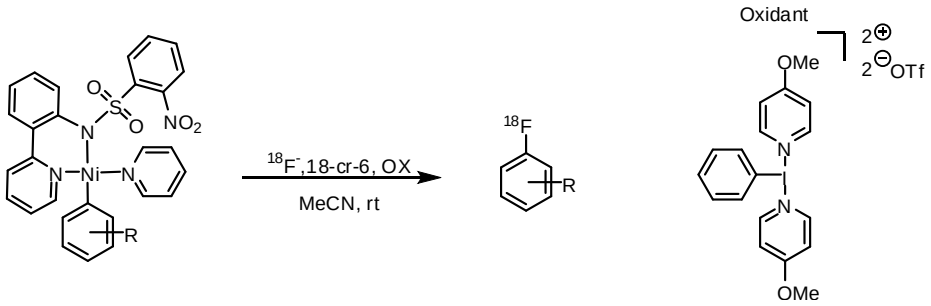
Gouverneur and co-workers reported the oxidative fluorination of *para-tert*-butylphenols with replacement of the *para-tert*-butyl group with ^{18}F-fluoride in the presence of iodobenzene diacetate and trifluoroacetic acid in dichloromethane with the radiochemical yields from 7 to 21% (Scheme 67).[148] The reaction tolerates a wide range of electronically diverse *ortho* substituents such as halides, other *tert*-butyl groups, carbonyl groups, and olefins (Scheme 67).



Scheme 67. Oxidative radiochemical fluorination of *para-tert*-butylphenols.

Recently, Ritter and co-workers reported a useful late stage methodology fluorination mediated by Ni (II) complex. Aryl pyridylsulfonamide complexes can be oxidized with the hypervalent iodine in the presence of aqueous ^{18}F-fluoride to obtain complex ^{18}F-labeled arenes in 13‑58% radiochemical yield (Scheme 68).[149] Radiofluorination reaction takes place at room temperature and is complete within less than one minute.

[147] Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639.
[148] Gao, Z.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 6733.
[149] Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456 ‑ 17458.



Scheme 68. Synthesis of ^{18}F-labeled aryl fluorides from Ni (II) complexes.

Nucleoside derivatives represent a class of biomarkers for PET imaging. They are used for the early detection of various cancers and the evaluation of treatment response to chemically related nucleoside analog prodrugs.[150] Nucleoside analog prodrugs are indicated for many types of cancer but generally have low response rates and can create significant side effects. Gemcitabine (Figure 12, **a**) is used for chemotherapy of some solid tumors such as pancreatic, non-small-cell-lung, breast and bladder cancer but generally shows a low response rate (rarely exceed 20% in pancreatic, ovarian and lung cancers)[151] and a grade 3 or 4 toxicity occurred in up to 38% of patients. Recently, new cytidine-based PET probes have been proposed, one of which is 1-(2'-deoxy-2'-fluoroarabinofuranosyl) cytosine (^{18}F-FAC) (Figure 12, **b**).[152]

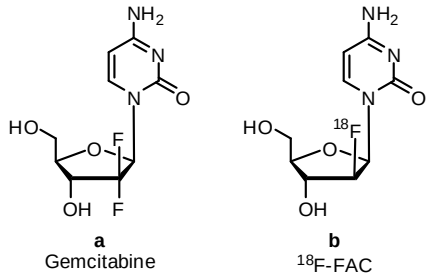
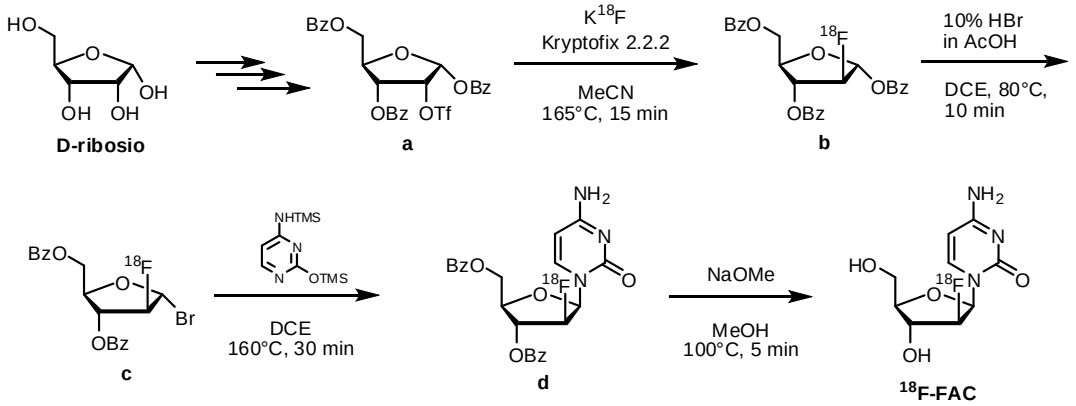


Figure 12. Chemical structure of the anticancer drug gemcitabine and cytidine-based biomarker.

This probe shows a similar chemical structure to gemcitabine, has a high affinity for deoxycytidine kinase (dCK), which represents the rate-limiting enzyme for the gemcitabine conversion from an inactive prodrugs to a citotoxic compound. Hence, *in vivo* studies with ^{18}F-FAC PET can indentify dCK- positive and -negative tumors and predict response to gemcitabine.[153] Thus, ^{18}F-FAC can be used effectively to personalize chemotherapy for

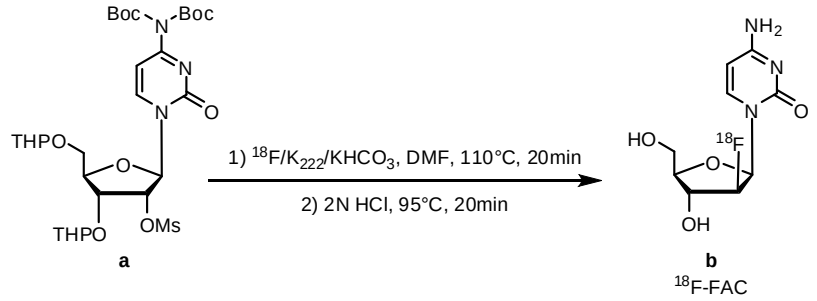
[150] a) Meyer, J.-P.; Probst, K. C.; Westwell, A. D. *J. Label. Compd. Radiopharm*.**2014,** *57*, 333–337.b) Shields, A. F. *J. Nucl. Med.* **2003,** *44*, 1432–1434.
[151] a) Colucci, G.; Giuliani, F.; Gebbia, V.; Biglietto, M.; Rabitti, P.; Uomo, G.; Cigolari, S.; Testa, A.; Maiello, E.; Lopez, M. *Cancer.* **2006,** *24*, 902-910. b) Heinemann, V.; Quietzsch, D.; Gieseler, F.; Gonnermann, M.; Schönekäs, H.; Rost, A.; Neuhaus, H.; Haag, C.; Clemens, M.; Heinrich, B.; Vehling-Kaiser, U.; Fuchs, M.; Fleckenstein, D.; Gesierich, W.; Uthgenannt, D.; Einsele, H., Holstege, A.; Hinke, A.; Schalhorn, A.; Wilkowski, R. J Clin Oncol. **2006**, *24*, 3946-3952.
[152]. Radu, C. G; Shu, C. J.; Nair-Gill, E.; Shelly, S. M.; Barrio, J. R.; Satyamurthy, N.; Phelps, M. E.; Witte, O. N. *Nat. Med.* **2008,** *14(7)*, 783–788.
[153] Laing, R. E.; Walter, M. A.; Campbell, D. O.; Herschman, H. R.; Satyamurthy, N.; Phelps, M. E.; Czernin, J.; Witte, O. N.; Radu, C. G. *Proc.Natl. Acad. Sci. U. S. A.* **2009**, *106*, 2847–2852.

cancer patients. ^{18}F-FAC has been synthesized previously but the insufficient reliability and reproducibility so far has prevented the wide use of ^{18}F-FAC.[154] The synthesis starts from D-ribose that in converted into triflate intermediate (Scheme 69, **a**) in several steps. ^{18}F is inserted by nucleophilic fluorination reaction, and the subsequent *N*-glycosidic bond formation reaction occurs on the activated compound (Scheme 69, **c**). The final deprotection of the benzoyl groups affords ^{18}F-FAC.



Scheme 69. Early stage strategy for the synthesis of ^{18}F-FAC.

Recently, Westwell and co-workers have reported the first example of late stage synthesis of ^{18}F-FAC with radiochemical yields of 4.3-5.5% and purities of more than 98% with a synthetic time of 168 min.[155] The ^{18}F-incorporation stage is a nucleophilic fluorination on 2'-position with a mesylate such as a leaving group, following a short deprotection (2N HCl for 20 min) step that decreases the final yields of the product ^{18}F-FAC. The best conditions for the key reaction are shown in Scheme 70.



Scheme 70. Radiofluorination of precursor and subsequent deprotection for the synthesis of ^{18}F-FAC.

The N-*bis*-Boc protection of **a** Scheme 70**,** is worth mentioning. The protecting group strategy was the result of extensive optimization to avoid dehydration of the precursor. Any less electron withdrawing protecting group led to a nucleophilic attack of the 2-oxygen on citydine

[154] a) Wu,C.-Y.; Chan,P.-C.; Chang, W.-T.; Liu, R.-S.; Alauddin, M., M.; Wang, H.-E. *Appl. Radiat. Isot.* **2009**, *67*, 1362-1365. b) Turkman, N.; Paolillo, V.; Gelovani, J. G.; Alauddin, M. M; .*Tetrahedron* **2012**, *68*, 10326–10332.

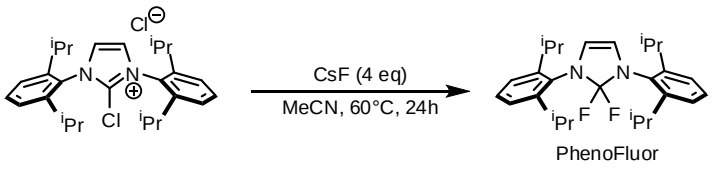
[155] Meyer, J-P; Probst, K.C.; Trist, I. M. L.; McGuigan, C.; Westwell, A. D. *J. Label Compd. Radiopharm* **2014**, *57*, 637-644.

into the 2'-position. However, even the optimized conditions do not yields enough ^{18}F-FAC for the synthesis to be practical.
The aim of this work is to synthesize a useful precursor for a distinct late-stage fluorination approach to develop an available and practical method in term of shortly, reliable, high-yielding of ^{18}F-FAC.

9.2 Results and discussion

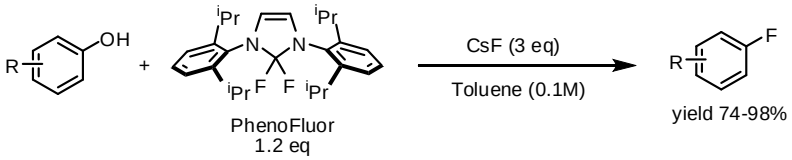
9.2.1 Deoxyfluorination with PhenoFluor

PhenoFluor is a deoxyfluorination reagent that was reported for the first time in 2011 by the Ritter group.[156] Currently, it is commercially available from Sigma-Aldrich and Strem Chemicals Inc.. The new deoxyfluorination reagent was prepared starting from *N,N*-diaryl-2-chloroimidazolium chloridewith CsF (Scheme 71). [157]



Scheme 71. Synthesis of PhenoFluor.

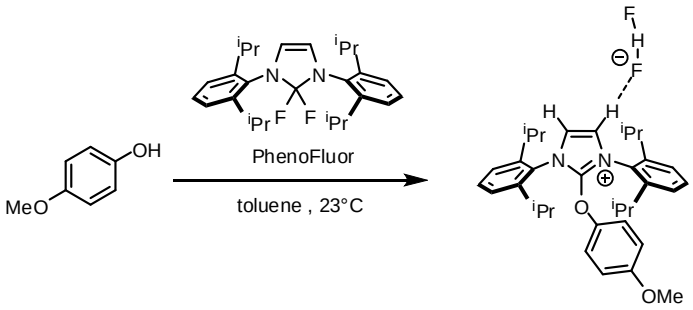
PhenoFluor is able to convert a wide variety of phenols (Scheme 72), including electron-rich arenes upon heating at 110 °C for 20 h.



Scheme 72. Deoxyfluorination of Phenols with PhenoFluor.

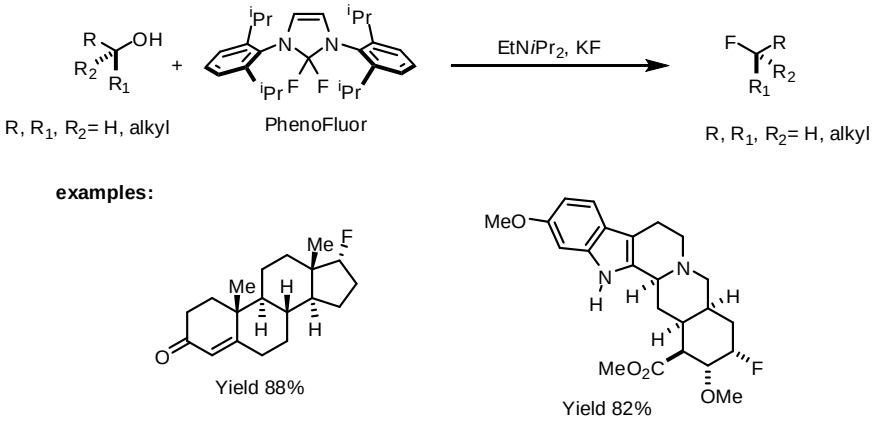
The mechanism for the deoxyfluorination takes into account the formation of 2-phenoxyimidazolium bifluoride salt formed from the reaction between phenol and PhenoFluor. The intermediate, formed from the condensation reaction of 4-methoxyphenol with PhenoFluor, could be isolated in 91% yield (Scheme 73).[156]

[156] Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc* **2011**; *133*, 11482-11484.
[157] Mendoza-Espinosa, D.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2010**, *132*, 7264.



Scheme 73. Formation of 2-phenoxyimidazolium bifluride salt.

Also, the deoxyfluorination of structurally complex aliphatic alcohols it is possible with PhenoFluor (Scheme 74).[158]



Scheme 74. Late-Stage Deoxyfluorination of Alcohols with PhenoFluor.

The high functional group tolerance and the possibility to use alcohols as a starting material makes PhenoFluor a particularly valuable tool for pharmaceutical application. As a consequence, a translation of this method into ^{18}F-radiochemistry was developed. To assess whether this methodology was applicable to ^{18}F-FAC, a precursor **16** (Figure 13) was prepared staring from cytidine **10** in 6 steps and 8.3% of overall yield. The synthetic pathway is shown in Scheme 75.

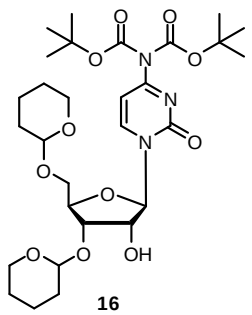
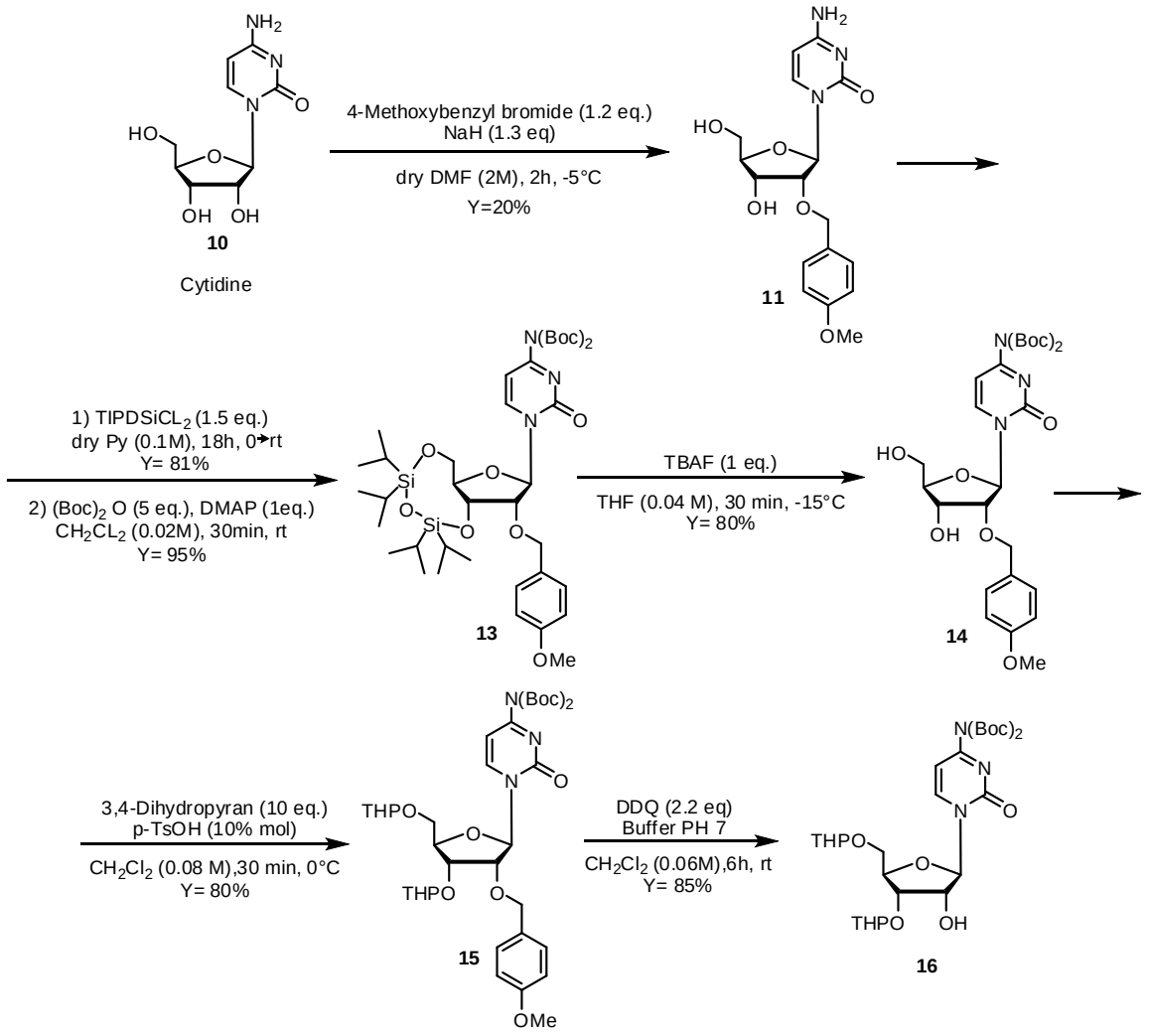


Figure 13. Chemical structure of precursor 16.

[158] Sladojevich, F.; Arlow, S.,I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc* **2013**; *135*, 2470-2473.

The first step of the synthesis is a selective 2'-protection of cytidine using 4-methoxybenzylbromide with NaH and the compound **11** was isolated by crystallization from water/EtOH mixture. Hereafter the compound **13** was carried out with selective 3'- and 5'-protection using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$) in pyridine followed by double N^4-Boc protection. TBAF- mediated removal of the bidentate-protecting group had to be carried out at lower temperature (-15 °C) in order to avoid the single Boc-group removal. Purified compound **14** was then converted into fluorination precursor **16** using 3,4-hydro-6H-pyran in excess and cleavage of PMB protecting group with DDQ.

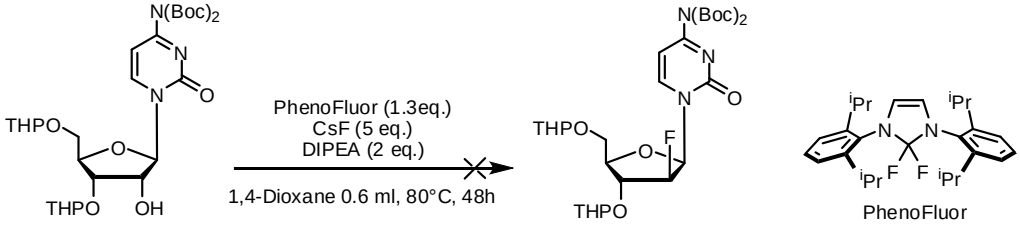


Scheme 75. Synthetic pathway for the precursor 16.

The precursor was designed to have a twofold N^4-Boc protection to reduce the electron density at the 2-carbonyl oxygen, while 3'/5'O-THP protection was chosen to reduce the side reaction observed in presence of electron withdrawing protecting group like benzoate. In fact, in previous fluorination reactions with PhenoFluor and a precursor with 3'/5'O-Bz protection, only the benzoyl fluoride was observed as a product.

In order to obtain a precursor that was as simple as possible, the synthesis of a methyl ether as the protecting group for the 3'- and 5'- O position was attempted. Unfortunately, the product was not stable and decomposed during the purification.

Finally, the fluorination reaction was tested on the precursor **16**. The reaction conditions have been summarized in Scheme 76.



Scheme 76. Deoxyfluorination condition with PhenoFluor.

After 48h at 80°C only starting material is present and no traces of any fluorinated products were observed. We hypothesized that the 2'-OH is not accessible due to steric hindrance and the imidazolium bifluoride salt, the key intermediate in the fluorination reaction, is not formed.

9.2.2 Fluorination by Manganese-Catalyzed Decarboxylation

In 2015, Groves and coworkers reported the first decarboxylative fluorination with fluoride, promoted by manganese porphyrin complexes (Figure 14).[159]

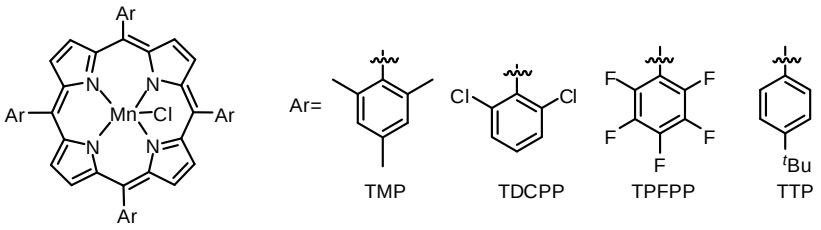
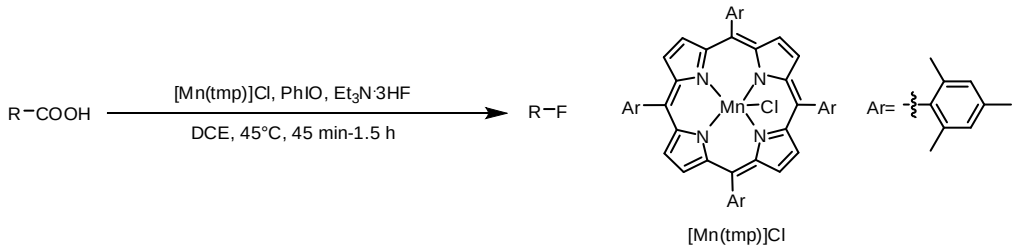


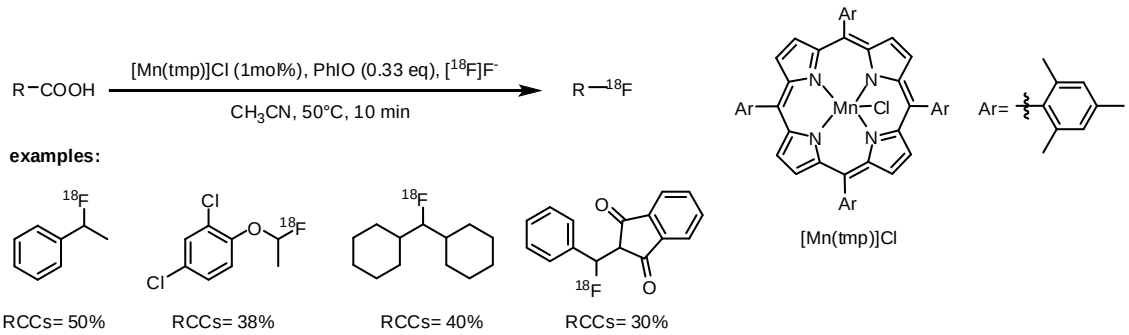
Figure 14. Chemical structure of the manganese porphyrin complexes.

The method is able to convert aliphatic carboxylates to the corresponding fluoride (Scheme 77). The substrate scope shows that a variety of functional groups, including heterocycles, esters, ether halogens and others are well tolerated and the best result in term of yield was achieved by using substrates with electron-donating substituents. Very important was the application of this methodology F^{18} radiochemistry (Scheme 78).

[159] Huang, X.; Liu, W.; Hooker, J. M.; Groves, J. T *Angew. Chem. Int. Ed* **2015,** *54,* 1-6.



Scheme 77. Decarboxylative fluorination manganese catalyzed.



Scheme 78. Manganese-catalyzed decarboxylative fluorination to ^{18}F labeling. Radiochemical conversion (RCCs) are averaged over *n* experiments.

Based on these results, a secondary carboxylic acid precursor for the synthesis of ^{18}F-FAC was developed. The carboxylic acid precursor **26** (Figure 15) was prepared staring from uridine **17** in 9 steps and 2.5% of overall yield.

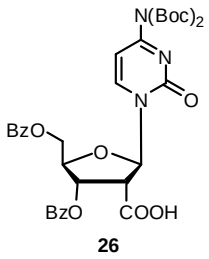
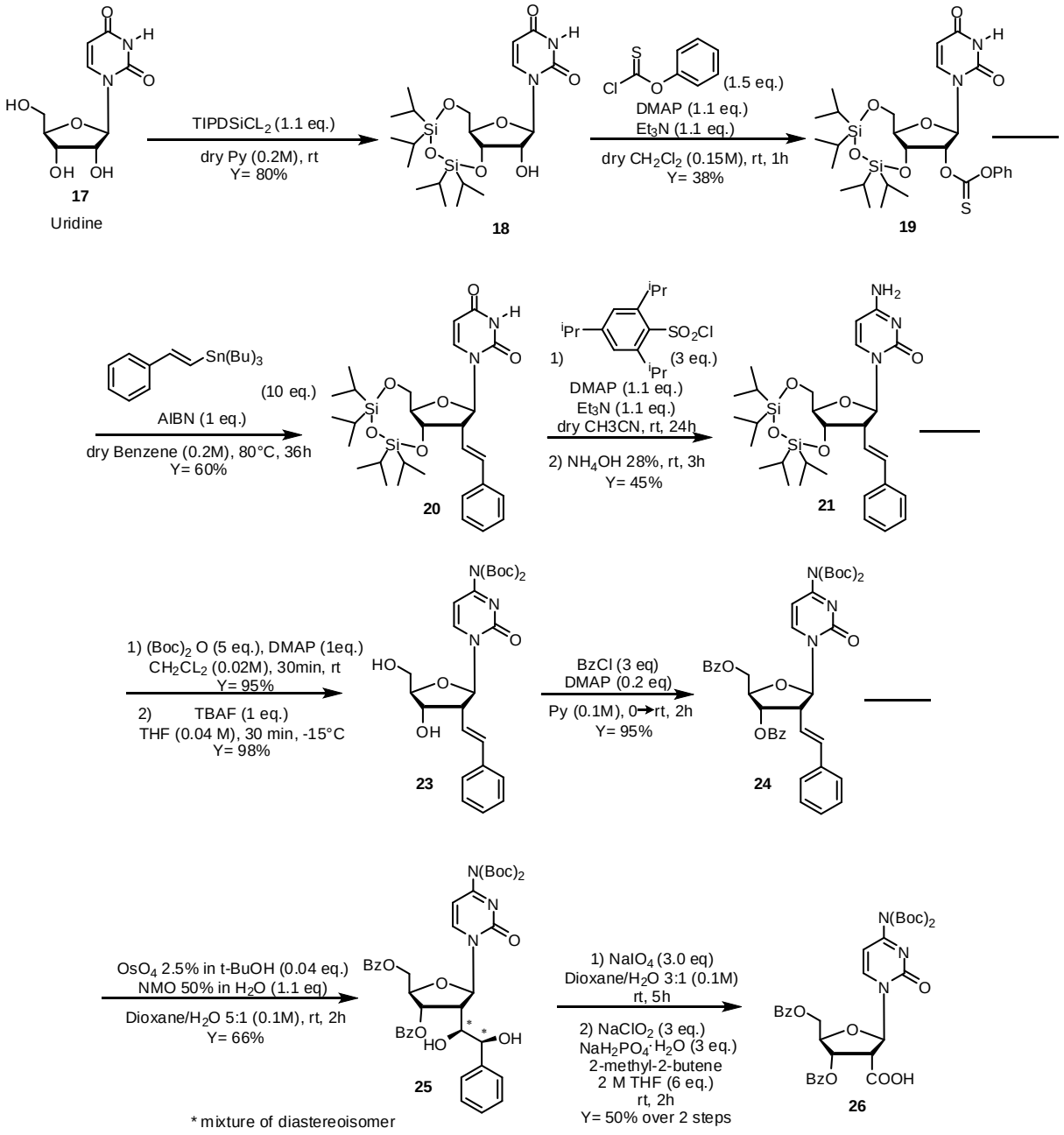


Figure 15. Chemical structure of precursor 26

The synthetic pathway, depicted in the Scheme 79, is based on the synthesis of a carboxylic acid cytidine derivative for decarboxylative fluorination mediated by Pd(IV)F attempted by Chiara Lambruschini in previous report of Ritter's research group.



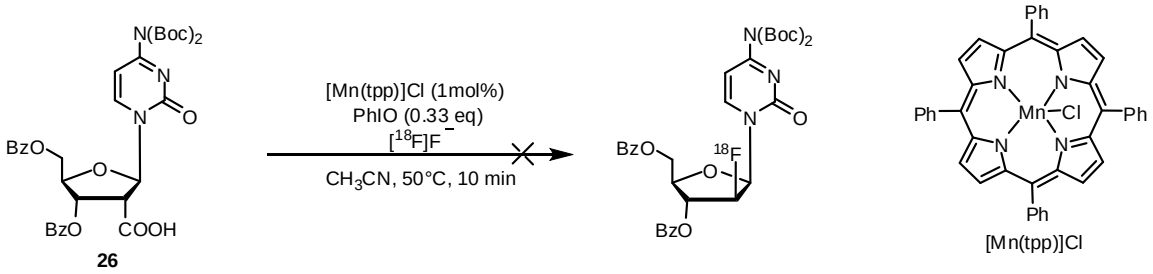
Scheme 79. Synthetic pathway for the precursor 26.

Uridine **17** was protected under classical condition with the Markiewicz reagent end 2' position was activated as Barton-McCombie thionocarbonate to give the product **19** for the subsequent radical reaction. The **19** was treated with (*E*)-tributylstyryltin, preparated by hydrostannylation of phenylacetylene with Bu_3SnH,[160] in high excess and in the presence of AIBN. The desired product **20** was obtained in 60% yield. The conversion into cytidine derivative **21** was carried out on the intermediate **20** by two steps reaction sequence consisting in triisopropylbenzenesulfonylation of the *O*-4 position of **20**, followed by treatment with concentrated ammonia. The synthesis of compound **24** was carried out with selective 3'- and 5'-protection using benzoyl chloride on the compound **23** with the bis N^4-Boc protection. The

[160] Labadie, J. W.; Tueting, D.; Stille, J. K., *J. Org. Chem.* **1983,** *48* (24), 4634–4642.

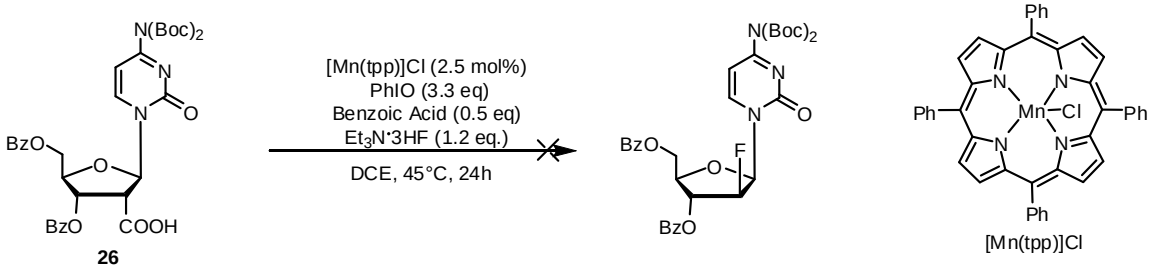
diol **25**, as mixture of diastereoisomers (*syn* addition), was obtained by dihydroxylation of the double bond with OsO_4 and *N*-methylmorpholine *N*-oxide. The C-C bond of the diol **25** was cleaved with $NaIO_4$ without the isolation of the resulting aldehyd. The desired compound **26** was attained by means of the Pinnick.

Finally the decarboxylative fluorination manganese-catalyzed reaction was tested on the precursor **26** for ^{18}F labeling. The reaction conditions are summarized in Scheme 80.



Scheme 80. Decarboxylative ^{18}F-fluorination reaction.

No traces of any radiolabelled product were observed and only starting material were recovered. To confirm this result, the catalytic decarboxylative fluorination based on nucleophilic fluoride was attempted on carboxyl acid cytidine derivative **26**. The reaction conditions are summarized in Scheme 81.

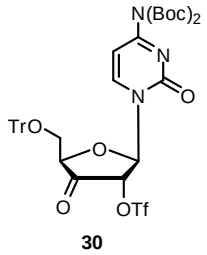


Scheme 81. Decarboxylative fluorination reaction.

After 24 h only the starting material was present and no trace of the fluorinated product was observed (Scheme 81)

9.2.3 Synthesis of 3'ketone Cytidine Derivative for Nucleophilic Fluorination Reaction

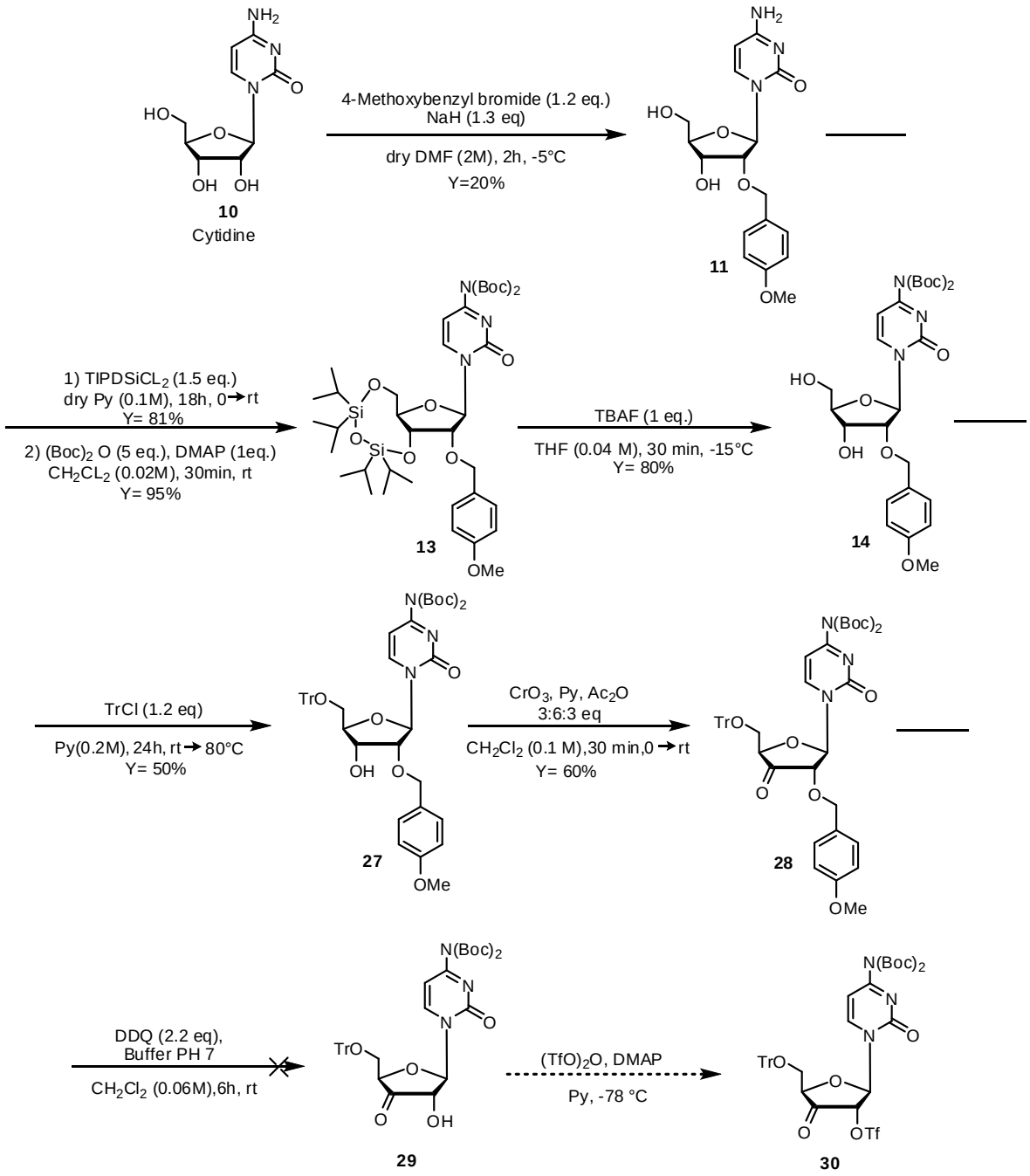
In order to obtain a precursor for a more efficient nucleophilic substitution, we attempted to develop strategies for the synthesis of a 3'ketone cytidine derivative **30** (Figure 16)



30

Figure 16. Chemical structure of precursor 30

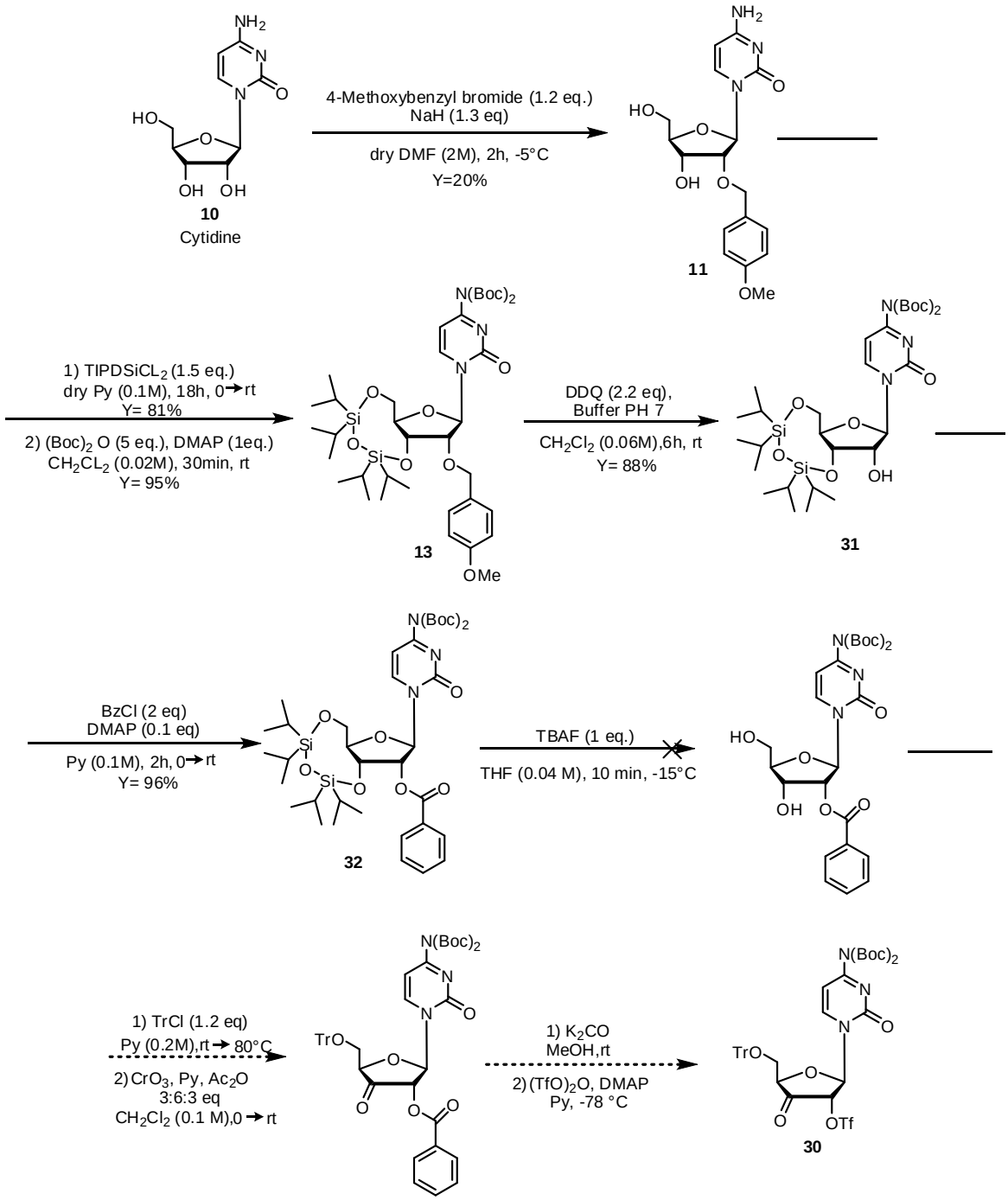
This compound should undergo a fluoride substitution in a much faster way than **16**. The π-orbital of the double C-O bond is aligned with the orbitals of the forming carbon-nucleophile and the breaking carbon-nucleofuge bond, stabilizing the transition stage and hereby accelerating the reaction. After the ^{18}F-fluorination reaction on the 3'ketone cytidine derivative, it is necessary to reduce the ketone to the alcohol and deprotect the product.
The first approach for the synthesis of the precursor **30** is reported in the Scheme 82.



Scheme 82. First approach for the synthesis of the precursor 30.

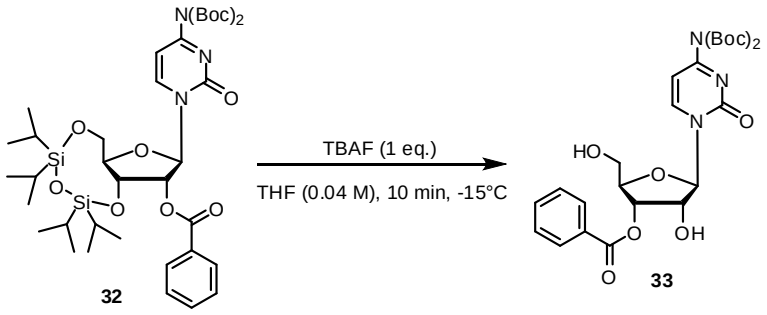
The first four steps of the synthetic pathway were the same for the compound 14 reported into the Scheme 75. Hereafter the selective protection of 5'- *O* position is obtained thanks to the reaction with triphenylmethyl chloride in pyridine of the compound **14**. For the oxidation step of the 3' hydroxyl group **27** different oxidative conditions were tested and the best result was obtained with CrO_3/Py/AcO_2. Despite the efforts, the cleavage of PMB protecting group with DDQ was not achieved without degrading the trityl protecting group.

A second approach for the precursor **30**, which avoids the use of oxidatively unstable protecting group (trityl), is reported in the Scheme 83.



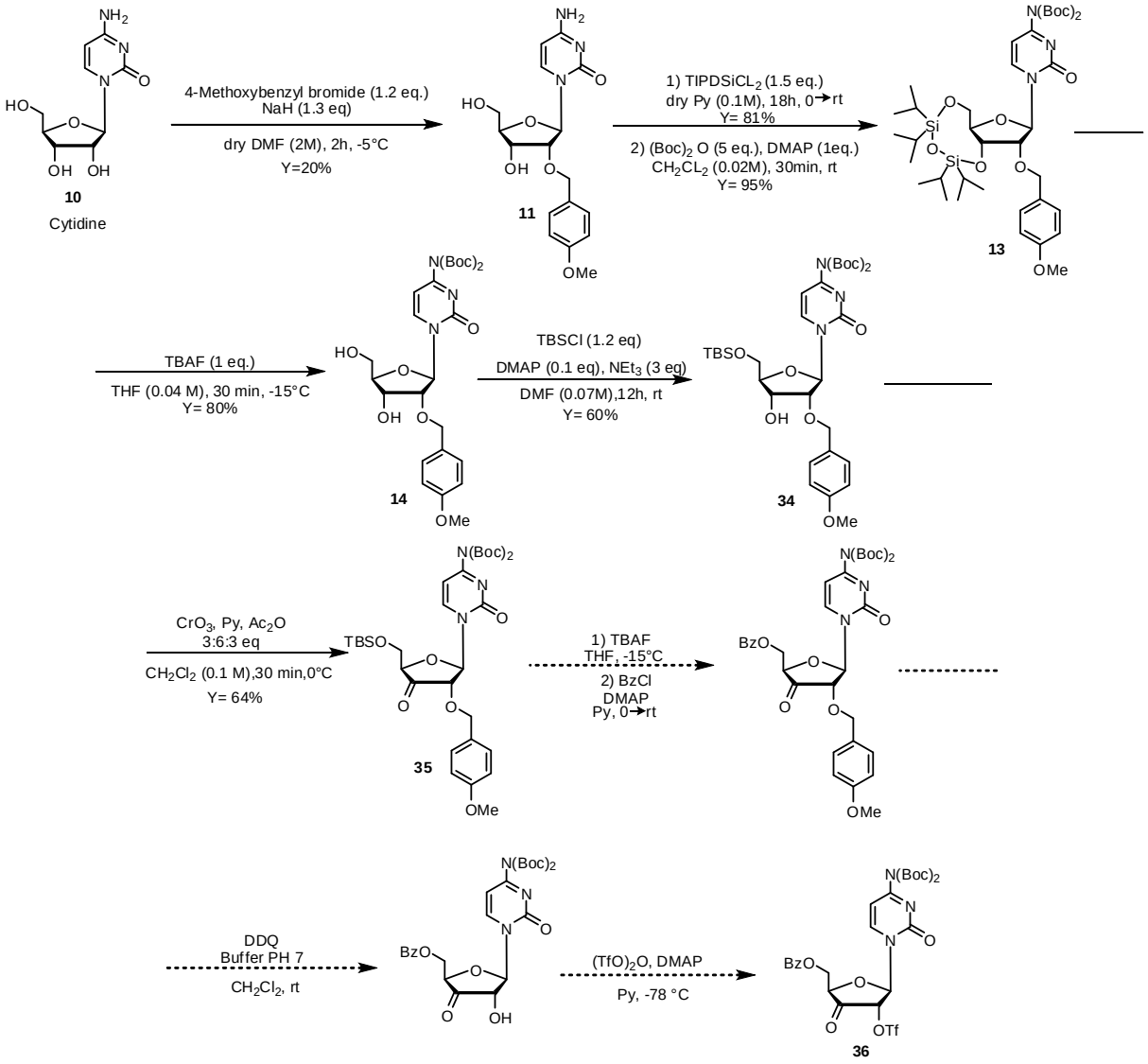
Scheme 83. Second approach for the synthesis of the precursor 30.

In this synthetic pathway, after a cleavage reaction of PMB protecting group with DDQ of the compound **13** and the selective protection of hydroxyl group with benzoyl chloride, the TBAF causes the shift of benzoyl group to the 3'-hydroxyl group (Scheme 84)



Scheme 84. Reaction of compound 13 in presence of TBAF.

In order to bypass this problematic steps (Scheme 84), a new approach was proposed. The synthesis pathways was reported in Scheme 85 for the precursor **36**. The first six steps have been carried out successfully up until **35**. In the protection of 5'-hydroxyl group of compound **14** was used trimethylsilyl chloride and then the oxidation of 3'-hydroxyl was successfully obtained with the same condition describe previously (CrO_3/Py/Ac_2O). The next step of the synthesis will be represented by a substitution of TBS protecting group with benzoyl and cleavage step of DDQ, following by the reaction of the formation of a good leaving group (as triflate) on 2' position.



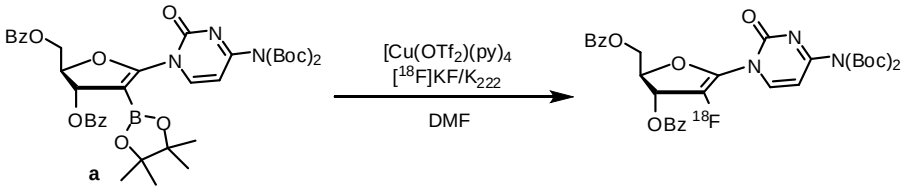
Scheme 85. Synthetic pathway for the precursor 36.

9.3 Conclusion and Future directions

We tried to synthesize a useful precursor for a the preparation of ^{18}F-FAC, a new and promising PET tracer, for a distinct fluorination methodology. Although the efforts for the synthesis of precursors, in both case no fluorination reaction took place. In 2014 Gouverneur and coworkers reported an efficient method for the synthesis of ^{18}F arenes in high radiochemical yields from pinacol-derived aryl boronic esters upon treatment with [^{18}F]KF/K_{222} and [$Cu(OTf)_2(py)_4$].[161] In the paper they also reported an example of fluorination reaction on alkenylBpin precursor for the preparation of ^{18}F-fluoroalkene derivates. This methodology might be amendable for the synthesis of ^{18}F-FAC together with

[161] Tredwell, M.; Preshlock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur V. *Angew. Chem. Int. Ed.* **2014**, *53*, 7751.

the proposed nucleophilic substitution by fluoride on 3'ketone cytidine derivative. In the Scheme 86 is reported the hypothetical Gouverneur Cu^{II}-mediated ^{18}F fluorination of cytidine **A** for the synthesis of ^{18}F-FAC precursor. After the ^{18}F-fluorination a hydrogenation reaction will be together with the overall deprotection of the product.



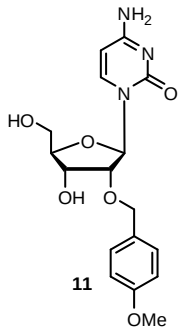
Scheme 86. Cu^{II}-mediated ^{18}F fluorination of pinacol-derived derived ester with ^{18}F fluoride

9.4 Experimental Section

9.4.1 General Information

All air- and moisture-sensitive reactions were carried out under nitrogen atmosphere. All light-sensitive reactions were carried out in amber vials. All the commercial available reagents were used as purchased from vendors without further purification. (*E*)-tributylstyryltin was synthesize according with literature procedure.[160] 1-(bromomethyl)-4-methoxybenzene was produced according with literature procedure.[162] Dry pyridine, 1,4-dioxane, dimethyl sulfoxide and dimethylformamide were used as received. Toluene was further degassed with nitrogen for 1 h before use. Thin layer chromatography (TLC) was performed using EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F_{254} plates and visualized by fluorescence quenching under UV light, $KMnO_4$ stain, ceric ammonium molybdate (CAM) stain and 2,4-DNP. Flash chromatography was performed using silica gel (230-400 mesh) purchased from Silicycle Inc. All isolated yields refer to pure products. NMR spectra were recorded on either a Varian Unity/Inova 600 spectrometer operating at 600 MHz for ^{1}H acquisitions, a Varian Unity/Inova 500 spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C acquisitions, respectively, or a Varian Mercury 400 spectrometer operating at 400 MHz and 375 MHz for ^{1}H and ^{19}F acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H: $CDCl_3$, 7.26). Data are reported as follows: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m= multiplet; coupling constants in Hz; integration. Spectra were acquired at 300 K. All deuterated solvents were purchased from Cambridge Isotope Laboratories. LC/MS data were obtained using a Shimadzu LCMS-2020.

9.4.2 Deoxyfluorination with PhenoFluor: Synthesis for the Precursor 16

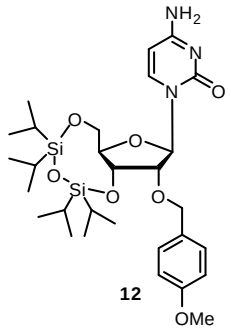


11

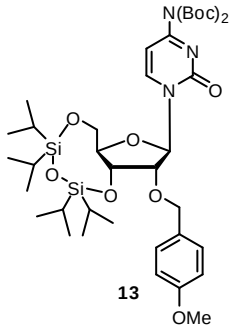
Cytidine **10** (121 mg) was dissolved in dry DMF (4.5 ml) and the solution was cooled at 5°C. NaH (1.3 eq, 15.6 mg, weighed at inert atmosphere) was added at this temperature. After 1h, 1-(bromomethyl)-4-methoxybenzene (1.2 eq, 121 mg) was added as a solution in DMF (0.5 ml) into a solution mixture. After 2h, the reaction was quenched with water and concentrated

[162] Kiruthika, S. E.; Perumal, P. T. Org. Lett **2014**, *16*, 484.

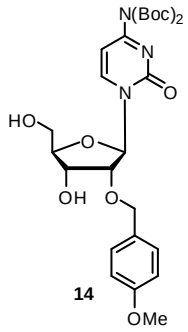
in vacuum. The resultant oil was dissolved in water and extracted with DCM. The aqueous phase was evaporated. The product **11**was crystallized from a solution water/EtOH.
^{1}H NMR (600 MHz, dmso) δ 7.84 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 29.4 Hz, 2H), 6.90 – 6.81 (m, 2H), 5.90 (d, J = 3.7 Hz, 1H), 5.65 (d, J = 7.4 Hz, 1H), 5.14 – 4.98 (m, 2H), 4.59 (dd, J = 26.8, 11.7 Hz, 2H), 4.07 – 3.99 (m, 1H), 3.84 (dt, J = 6.0, 2.9 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.72 (d, 3H), 3.60 (m, 2H).



$TIPDSCl_2$ (1.38 mmol, 0.479 ml) was added a solution of the compound **11** (1.09 mmol, 400 mg) dissolved into pyridine (13 ml) at 0°C under N_2. The reaction was left under stirring overnight at room temperature. The reaction was quenched with $NaHCO_3$ saturated solution and extracted with DCM. The product **12** was isolated after column chromatography on silica gel (DCM/MeOH 2% then DCM/MeOH 3%) (Y=77%)
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, 7.5 Hz, 1H), 7.42 (d, *J* = 7,4 Hz, 2H), 6.90 – 6.80 (m, 2H), 5.91 – 5.84 (m, 1H), 5.66 (d, *J* = 7.4 Hz, 1H), 5.33 – 5.26 (m, 1H), 4.93 (dt, *J* = 40.6, 12.7 Hz, 2H), 4.31 – 4.16 (m, 2H), 4.10 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.95 – 3.88 (m, 1H), 3.82 – 3.75 (m, 3H), 1.19 – 0.72 (m, 28H).



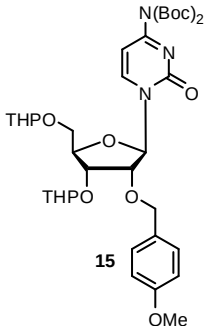
Di-*tert*-butyl dicarbonate (5 eq,180 mg) and DMAP (1 eq. 20.16 mg) were added a solution of the compound **13** (0.165 mmol, 100 mg) dissolved into DCM (7.5ml). The reaction was left under stirring for 30 min at room temperature. The reaction was quenched with water and extracted with DCM. The product **13** was isolated after column chromatography on silica gel (Hexanes: AcOEt 80:2) (Y= 98%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 7.6 Hz, 2H), 6.90 – 6.78 (m, 2H), 5.85 (s, 1H), 4.91 (d, J = 3.1 Hz, 2H), 4.25 (m, 2H), 4.04 – 3.90 (m, 2H), 3.78 (s, 3H), 1.56 (s, 12H), 1.19 – 0.72 (m, 28H).



14

The compound **13** (806 mg) was dissolved in THF (4ml). TBAF (1M in THF, 1 eq) was added a low temperature (-15°C). After 30 min no starting material is present and the solvent was removed *in vacuum*. The product **14** was isolated after column chromatography on silica gel (DCM: MeOH 4%) (Y= 77%).

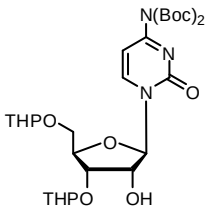
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.03 (m, 1H) 7.28 (d, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 7.5 Hz, 2H), 6.90 – 6.82 (m, 2H), 5.84 – 5.69 (m, 1H), 4.99 – 4.61 (m, 2H), 4.35 – 4.28 (m, 1H), 4.28 – 4.17 (m, 1H), 4.12 – 3.97 (m, 2H), 3.91 – 3.81 (m, 1H), 3.81 (m, 3H), 2.86 (bs, 1H), 2.69 – 2.57 (m, 1H), 1.57 (s, 12H).



15

3,4-Dihydro-2H-pyran (10 eq, 0.069 ml) and p-TsOH (0.1 eq. 1.30 mg) were added a solution of the compound **14** (0.165 mmol, 100 mg) dissolved into ACN (0.7 ml) at 0 °C The reaction was left under stirring for 1h at 0 °C. The reaction was quenched with water and extracted with DCM. The product **15** was isolated after column chromatography on silica gel (Hexanes: AcOEt 90:10 to 70:30) (Y= 79%).

^{1}H NMR (600 MHz, $CDCl_3$) difficult interpretation for the presence of 4 diastereoisomers. The result was confirmed by LCMS Mw: 731.36



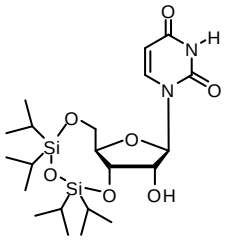
16

DDQ (2.2 eq, 0.132 ml) and a buffer solution were added a solution of the compound **15** (0.0602 mmol, 44.1 mg) dissolved into DCM (1.7 ml) at rt The reaction was left under stirring overnight at rt. The reaction was quenched with $NaHCO_3$ saturated solution and extracted

with DCM. The product **16** was isolated after column chromatography on silica gel (Hexanes: AcOEt 90:10 to 70:30) (Y= 65%).
^{1}H NMR (600 MHz, $CDCl_3$) difficult interpretation for the presence of 4 diastereoisomers. The result was confirmed by LCMS Mw: 611.31.

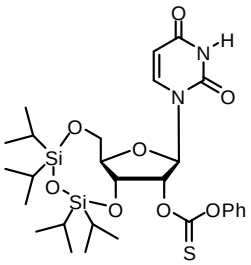
In inert atmosphere In a NMR tube the compound **16** was transferred and dissolved with 1,4-dioxane (0.6 ml). CsF (5 eq, 13,1 mg) and *PhenoFluor* (1.3 eq, 9.6 mg) and DIPEA (2 eq, 4.5 mg) were added. The reaction mixture was left at 80ºC for 48h in a NMR tube. The reaction was monitored with ^{19}F NMR (375MHz, 23 ºC, 1,4-dioxane)

9.4.2 Fluorination by Manganese-Catalyzed Decarboxylation: Synthesis of the Precursor 26



18

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (1.1eq, 1.3 ml) was added to a solution of uridine (2.00 g, 8.2 mmol) in dry pyridine (36mL) at rt under N_2. The reaction was stirred until completion (2 h). Pyridine was removed under reduced pressure. The residue was dissolved in DCM and poured in NH_4Cl saturated solution. The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude was purified by chromatography eluting with DCM/acetone 92:8 + 1% of *i*PrOH to afford the desired compound (1.9 g, 49%)
^{1}H NMR (399 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 5.73 (s, *J* = 6.4 Hz, 1H), 5.70 (d, *J* = 8.1 Hz, 1H), 4.37–4.08 (m, 4H), 3.99 (d, *J* = 13.0 Hz, 1H), 3.70 (s, 1H), 1.19–0.85 (m, *J* = 20.2, 7.8 Hz, 28H).

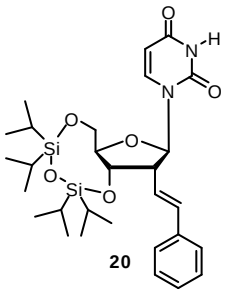


19

Et_3N (1.1 eq, 0.61 ml) was added to a solution of **18** (1.95 g, 4.01 mmol) and DMAP (1.1 eq, 0.54 g) in dry DCM (26 mL) at rt under N_2. Then *O*-phenyl chlorothionoformate (1.5 eq, 1.04g) was added dropwise at rt. Arter 1h the mixture was poured in saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic phase was dried over $MgSO_4$. After

evaporation of the solvent, the crude was purified by chromatography using hex/EtOAc 7:3 to afford the desired compound **19** (31%)

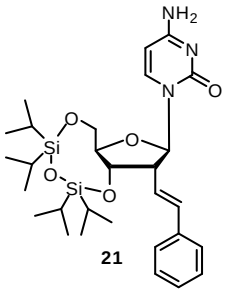
^{1}H NMR (399 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.01 (d, *J* = 4.6 Hz, 1H), 5.94 (s, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 4.55 (dd, *J* = 8.8, 4.6 Hz, 1H), 4.25 (d, *J* = 13.4 Hz, 1H), 4.10 (d, *J* = 9.0 Hz, 1H), 4.03 (d, *J* = 13.6 Hz, 1H), 1.19–0.90 (m, 28H).



20

Tributylstyryltin (10 eq, 5.41) was added to a solution of **19** (1g, 1.57 mmol) and AIBN (1 eq, 2.58g) in dry and degassed benzene (6.4 mL) under nitrogen at 40 °C in an amber vial. Then the septum was quickly replaced with a screw cap and the mixture was stirred at 80 °C for 36 h. After evaporation of the solvent. The desired compound **20** was purified by chromatography of crude using hex/EtOAc 7:3. (Y= 60%)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.41–7.37 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.26–7.22 (m, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.37 (dd, *J* = 16.1, 7.9 Hz, 1H), 6.00 (d, *J* = 3.2 Hz, 1H), 5.73 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.52 (t, *J* = 7.3 Hz, 1H), 4.12 (dd, *J* = 13.4, 4.5 Hz, 1H), 4.06–4.02 (m, 2H), 3.06 (td, *J* = 7.2, 2.4 Hz, 1H), 1.14–0.91 (m, 28H). MS (ESI) *m/z* calcd. for $C_{29}H_{44}N_2O_6Si_2$ $[M+H]^+$: 573; found: 573; $[M-H]^-$: 571; found: 571.

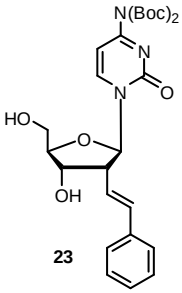


21

Et_3N (3eq, 85.8μL) was added to a solution of **20** (0.118 mg, 0.206 mmol), DMAP (3 eq, 75.5 mg) and 2,4,6-triisopropylbenzenesulfonyl chloride (3 eq, 0.187 mg) in dry MeCN (7.7 ml) under N_2 at rt. The mixture was stirred for 24 h, then NH_4OH (11.5 ml, 28% solution) was added and the mixture was stirred for 3 h at rt. The solvent was removed and the product was extracted with DCM. The organic phase was dried over $MgSO_4$ and filtered. After evaporation of the solvent, the crude was purified by chromatography using DCM:MeOH 4 % to afford the desired compound **21** (Y= 45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4 Hz, 1H), 7.44–7.37 (m, 2H), 7.33–7.27 (m, 2H), 7.25–7.19 (m, 1H), 6.81 (d, *J* = 16.0 Hz, 1H), 6.43 (dd, *J* = 16.1, 7.3 Hz, 1H), 6.05 (d, *J*

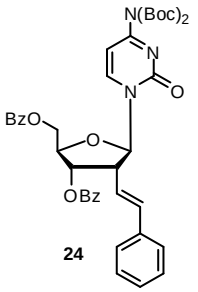
= 1.8 Hz, 1H), 5.65 (d, *J* = 7.4 Hz, 1H), 4.51–4.40 (m, 1H), 4.18 (dd, *J* = 13.3, 2.7 Hz, 1H), 4.07–3.97 (m, 2H), 3.16 (t, *J* = 7.0 Hz, 1H), 1.14–0.91 (m, 28H).



23

For the compound **23** the procedures for the two steps are the same describe for the compound **13** and **14**. The crude was purified by chromatography using DCM:MeOH 4 % to afford the desired compound **23** (Y= 93%).

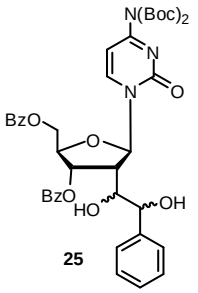
^{1}H NMR (600 MHz, cdcl$_3$) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.22 (m, 5H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 16.1 Hz, 1H), 6.25 (dd, *J* = 16.1, 8.7 Hz, 1H), 5.79 (d, *J* = 8.2 Hz, 1H), 4.55 (s, 1H), 4.23 (s, 1H), 3.98 (d, *J* = 2.1 Hz, 1H), 3.90 – 3.75 (m, 2H), 1.56 (s, 18H).



24

Benzoyl chloride (3 eq, 0.073 ml) was added to a solution of **23** (0.112 g, 0.212 mmol) and DMAP (0.2 eq, 5.18 mg) in dry Py (2 mL) at 0°C under N_2. Arter 3h the mixture was poured in saturated aqueous NH_4Cl solution and extracted with DCM. The organic phase was dried over $MgSO_4$. After evaporation of the solvent, The crude was purified by chromatography using DCM:MeOH 4 % to afford the desired compound **24** (Y= 92%).

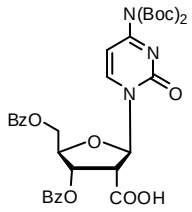
^{13}C NMR (151 MHz, cdcl$_3$) δ 168.78, 168.38, 164.96, 156.84, 152.07, 145.22, 138.84, 138.52, 136.33, 136.26, 132.71, 132.43, 132.23, 132.04, 131.66, 131.42, 131.28, 131.08, 131.00, 130.56, 129.28, 122.41, 99.72, 91.54, 87.69, 84.78, 79.12, 66.82, 55.60, 30.32.



25

OsO_4 (97.8 μL, 0.0078 mmol, 2.5% wt in *t*BuOH) was added to a solution of **24** (144 mg, 0.195 mmol) and NMO (44.7 μL, 25.1, 50% wt in water) in dioxane/H_2O 5:1 (1.69 ml) in an

amber vial at rt. The reaction was stirred until completion (1.5 h). Na_2SO_3 (660 mg, 4.84 mmol) was added and the mixture was diluted with H_2O and EtOAc. The mixture was stirred for 30 min. Then the phases were separated. The organic phase was dried over $MgSO_4$. After evaporation of the solvent, the crude was purified by chromatography using hex/EtOAc 80:20 to 70:30 to afford the desired compound **25** (Y= 66%) as a mixture of diastereoisomers.
^{1}H NMR (600 MHz, $CDCl_3$) not clean interpretation. MS (ESI) *m/z* calcd. for $C_{41}H_{45}N_3O_{12}$ found: 771.8 confirmed the data.



26

$NaIO_4$ (3 eq, 78 mg) was added to a solution of **25** (94 mg, 0.12 mmol) in dioxane/H_2O 3:1 (1.22 ml) at rt. The reaction was stirred until completion (5 h). A white precipitate was present. The mixture was filtered and washed with THF. The solution was concentrated until the original volume. 2-methyl-2-butene (6 eq 0.36 ml 2.0 M in THF) was added to this solution. Then a solution of $NaClO_2$ (3 eq, 33 mg) and $NaH_2PO_4 \cdot H_2O$ (3 eq,50.4) in H_2O (400 μL) was added. The mixture initially yellow and became colorless overtime. The reaction was stirred until completion (2 h). The mixture was diluted with and extracted with DCM The organic phase was dried over $MgSO_4$. The crude was purified by chromatography using DCM:MeOH 5 % to afford the desired compound **26** (Y= 50%).
^{1}H NMR (600 MHz, dmso) δ 8.30 (d, *J* = 7.5 Hz, 1H), 7.97 (dd, *J* = 18.8, 7.6 Hz, 4H), 7.65 (t, *J* = 6.9 Hz, 2H), 7.51 (dd, *J* = 13.6, 7.4 Hz, 4H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.37 (d, *J* = 7.0 Hz, 1H), 5.74 (s, 2H), 4.62 (dd, *J* = 13.2, 7.6 Hz, 1H), 4.52 (d, *J* = 7.5 Hz, 2H), 1.48 (s, 15H).

[Mn(tpp)]Cl (2.5 mol%, 0.36 md), acid substrate 26 (14 mg, 0.020 mmol), $Et_3N \cdot 3HF$ (1.2 equiv, 3.9 μl), benzoic acid (0.5 eq, 1.22 mg), and DCE (0.040 ml) were added to the vial and heated to 45 °C. Under a stream of N_2, PhIO (3.3 equiv, 14,5 mg) was added to the mixture of reaction. The reaction was monitored with ^{19}F NMR (375MHz, 23 ºC, DCE).

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